HENRY FORD HOSPITAL MEDICAL BULLETIN

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HENRY FORD HOSPITAL MEDICAL BULLETIN

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EDITORIAL: THE HAZARDS OF MEDICAL IRRADIATION

ROBERT J. BLOOR, M.D.

Radiation is a toxic agent. This has been recognized for a half century as far as large quantities are concerned. The necrotizing effect on locally irradiated tissues and the lethal effect on the whole organism are known to layman and physician alike. The potential hazard of small exposures was first recognized from the cumulative effect noted in the pioneer radiologists, but again this involved large total doses. With further study the dose required to produce a recognizable effect has been found to be smaller and smaller. Even the low exposures in diagnostic procedures and the scattered radiation from therapeutic applications are not completely without hazard. The estimate that the medical use of radiation constitutes the single largest source of exposure to the population of this country has given rise to much concern.

Little is accurately known about the significance of small radiation doses. While there is evidence that exposure of certain parts of the body to as little as 5 to 10 rads may be damaging in some instances, the degree of this hazard, either to the individual or the population, is not clear. One of the basic sources of this confusion is the uncertainty that exists regarding the dose-effect relationship at very low levels. Virtually all of the experimental and clinical studies have been done at dose levels above 100 r, with extrapolation of the results to the low dose region.

There are several questions regarding the relation of dose to effect with small exposures that have not been satisfactorily answered. Is there a threshold dose that must be exceeded, *i.e.*, must a certain quantity of radiation be given before any effect is produced, or is the reaction "non-threshold" with respect to dose? Will repeated doses of radiation cumulate by simple summation or is there a more complex relationship? Will the same increase in dose always produce the same increase in effect (*i.e.*, is the relationship linear) or will the dose-effect relationship be more complex (nonlinear)? Until these questions can be answered, our information must remain qualitative rather than quantitative, and we are unable to assign accurate values to our estimates of hazard.

The induction of mutations as a result of radiation exposure is generally regarded as a linear, nonthreshold reaction, and the effects of repeated doses are thought to be cumulative by simple summation. Extensive studies of this genetic effect have been carried out in insects and small mammals. It is quite certain from the correspondence of effects in various species that the same qualitative effects occur in man, but the quantitative dose relationships remain uncertain. Estimates of the amount of radiation necessary to double the spontaneous mutation rate range from 20 to 80 or 100 rads. The greatest proportion of mutations are recessive; hence a mutated gene from one parent must join with a mutated gene from the other parent before the changed characteristic will be evident in the offspring. The frequency with which such junction can occur depends upon the number of mutations present in the breeding population. Thus the average radiation dose received by a breeding

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population is more important than that received by any one person. Mutation occurring after an individual's last child is conceived is of no significance either to the population or to his descendants.

Induction of neoplastic changes in body tissues is known to occur after exposure to moderate or large quantities of radiation. The evidence that this can occur at low radiation rates and total doses is largely indirect and depends heavily on the assumption that the dose-effect relationship is linear at all levels and without threshold. Actually, on the basis of experimental studies of the induction of cancer and leukemia, there are equally good reasons for considering this relationship as nonlinear or having a threshold. At any rate, because neither situation can be proved, the possibility exists that doses in the diagnostic exposure range might contribute to the induction of neoplasia and that this must be taken into account as a possible hazard. There is reason to think that infants and children may be more sensitive in this respect and therefore justify special consideration.

Shortening of the life span of experimental animals has been observed after prolonged irradiation at low dose rates. This is nonspecific in character without preponderance of any particular lesion. Attempts to evaluate this effect in man by consideration of the relative longevity of radiologists and other physicians has been inconclusive. At the present time there are insufficient data regarding this reaction in man to permit any estimate of the significance of the phenomenon clinically. It can probably be disregarded as far as medical exposure is concerned, though it must still be considered in relation to occupational exposure.

Production of fetal damage by irradiation in early pregnancy appears to present a more significant hazard than those so far mentioned. Doses of 5 to 10 rads applied to the mother during the early cleavage phases of the fertilized ovum can be shown to reduce litter size in experimental animals. Such doses will also increase the incidence of malformation to a measurable degree in the surviving fetuses. There is a reduction in this sensitivity with time of gestation; it remains higher in the first trimester than during the remainder of pregnancy. Women in the child-bearing age who may be pregnant thus constitute a particular problem. The recommendation that radiation exposure to the pelvis be avoided in such women except during the time from the onset of menstruation to the time of ovulation seems well taken.

Despite these uncertainties, quantitative estimates of radiation hazard have been made which can serve as a guide in practice. The most generally accepted estimate concerning genetic effect is that exposure of the gonads to 50 rads will double the spontaneous rate of mutation. The number of abnormalities that will appear in a population depends on the number of mutated genes present. There is an equilibrium between mutation induction and spontaneous loss. Thus to double the number of mutationally produced abnormalities would require exposure of an entire population to an average dose of 50 rads for the twenty to thirty generations necessary to establish equilibrium. Estimation of leukemogenic hazard depends on acceptance of a linear, nonthreshold relationship between dose and effect which is not on completely firm ground. On this basis, one can estimate that a dose of 30 rads to the whole hemato-

poietic volume would double the normal incidence of leukemia, *i.e.*, raise the probability of an individual's becoming leukemic from about 1:15,000 to 1:7,500. Insufficient data are available regarding other carcinogenesis to permit any estimate, however poor. The values given for the production of fetal abnormalities or abortion are minimum for the first two to four weeks of gestation. The apparent threshold value is about 15 to 20 r for the remainder of the first trimester and probably two or three times this amount for the remainder of gestation.

The most frequent source of radiation exposure in medicine is the diagnostic examination. Many studies have been made of this problem. Among the most striking observations that emerge from a study of these reports are the tremendous range of exposure that exists between one examination and another and the considerable variation of dose with variations in technic in the same type of examination. For example, the ovarian dose may vary from a low of about 0.02 mr for a chest examination to a total of about 7,000 mr for pelvimetry. With different technics and radiographic factors, the fetal dose received during a complete pelvimetric examination may vary from 2,000 mr to as high as 45,000 mr. Fluoroscopy presents some of the greatest possibilities for overexposure. The ovarian dose from an examination involving the pelvis may be as high as 30,000 to 40,000 mr when performed by an inexperienced examiner with unsuitable technic and antiquated equipment. The same examination carried out by an experienced fluoroscopist on good equipment will result in exposures of one-tenth of this amount or less.

Reduction of patient exposure is quite simple. Exclusion of the critical area from the direct beam by means of accurately adjusted diaphragms is more effective than any other factor. The use of high-kilovoltage technics and high-speed films and screens will reduce total exposure both in the beam and out. These should be employed whenever possible. Increased filtration at the tube-head is very effective in reducing skin exposure but has less effect on the dose received by tissues within the body. The addition of local shielding to the gonads adds rather little to the protection obtained from collimation, except where the reproductive organs are in the direct beam. Local shielding is helpful here if permitted by diagnostic considerations.

Very little information is available concerning exposure to the bone marrow. The meticulous and elegant studies that are being carried out by the physics group at Memorial Center in New York do much to dispel this lack. The reader is referred to the paper by Epp, Weiss, and Laughlin[1] which reports measurements of dose to the hematopoietic system resulting from chest examinations, and to a study by Holodny, Lechtman, and Laughlin on bone-marrow exposure during the application of radioactive materials to pelvic cancer (to appear in *Radiology* for July). These studies supply much needed data for evaluation of marrow exposure and leukemia hazard.

General patient exposure resulting from therapeutic irradiation appears to present a lesser problem. The radiation beams used are small and well collimated. A very high proportion of patients receiving such treatment are beyond the age when reproduction is possible. The greatest use of radiation therapeutically is in the treatment of cancer. The danger to life from the patient's malignant tumor is much

greater than that from the effects of radiation even if the possibility of the induction of cancer were much greater than it appears to be on clinical grounds.

Cancer is relatively rare in children and young adults, but this is the group in which gonadal exposure should be minimized. The papers by Kaplan, Collica, and Rubenfeld and by Gwinn, Gastineau, and Campbell in this issue of *Radiology* deal with the gonadal irradiation resulting from therapeutic application. The first presents tables relating gonadal exposure to field size and location for middle-energy x-rays. The value of local gonadal shielding is shown to be appreciable even with the well collimated beams used therapeutically. As would be expected, treatment of areas well removed from the gonadal region results in little genetic hazard. The paper by Gwinn *et al.* is concerned particularly with the irradiation of children. Using phantoms constructed to represent typical children of three ages, they studied gonadal dose from a variety of therapeutic procedures that had been used in their department. The dose received in the region of the reproductive organs in these various phantoms was quite low for most procedures. Treatment of the proximal femur in the male or the retroperitoneal region in the female were the only procedures delivering more than 50 rads to this critical area.

Very few objective data are available concerning the exposure received by the general population. The estimate that medical uses of radiation constitute the greatest source of such exposure, referred to earlier, is based on several assumptions. The paper by Morgan in this issue describes a measuring devicé that is simple to use which would permit the collection of exposure data on every patient receiving a diagnostic examination. A continuous record of such exposures on all patients in one or more departments would help materially in supplying population exposure data.

There is reason to suspect that radiation exposure even in the small amounts associated with diagnostic radiology may have some deleterious effects either on the individual or on the genetic constitution of the human race. The degree of this hazard cannot be defined from the information available. Each physician responsible for the operation of equipment used in medical radiology should make every effort to use technics that have been shown to reduce exposure, but should not hesitate to perform an examination that will be of clinical benefit to the patient. Particular care is necessary in the exposure of women in the reproductive age.

The use of radiation diagnostically and therapeutically is essential to the present-day practice of medicine. It should be used with care and with knowledge of the possible hazards. In this way it will continue to be of greater benefit than hazard.

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MY FRIEND, DR. ROY D. McCLURE*

JEAN PAUL PRATT, M.D.**

As one who knew Roy D. McClure, and was associated with him for most of his life, I feel that it is a great privilege to be asked to give this annual memorial lecture. Our first contact was when we were assembling in a French class at Ohio State University, where, in his characteristic manner, he introduced himself and our friendship began. From that time our association continued with brief interruptions, and therefore qualifies me to speak of my friend Roy D. McClure.

Previous lectures have recounted Dr. McClure's achievements as a surgeon. His valuable contributions to surgical societies and medical journals have been related and need not be repeated here. The chapter in his life which includes his education and preparation as a surgeon is probably not so well known to you. My association with him during those years permits me to recall some of the important events.

Construction of a building does not begin with the roof, but completion of the structure is possible only when a proper foundation is laid. Likewise, present day surgery did not suddenly appear, but the experience and contributions of the past have built a suitable foundation for the development of present methods. It is fitting, therefore, to inquire into some of the events of his earlier life which influenced his career. With your indulgence an attempt will be made to catch a glimpse of medicine as practiced and taught at that time, and try to show the influence of some of the teachers.

My impression is that there was no particular time at which Roy McClure decided to study medicine, but it was just assumed that he would follow the family tradition. His father, grandfather and great grandfather were doctors. I knew his father as a devoted physician who was in active practice to the last year of his life. He was justly proud of his son.

Although Roy was born in Bellville, Ohio the family moved to Columbus in time for his school and college education. When Roy entered Ohio State University in 1900 the total enrollment of that institution was slightly over 1200. The small classes had the great advantage of close contact of students with teachers. He especially liked Dean McPherson who was head of chemistry, and Landacre in biology. With the latter he took 3 courses, general zoology, comparative anatomy and embryology. In these courses a spirit of investigation and research was emphasized rather than memorization. This was a good foundation for his future study of medicine. Perhaps, also this spirit accounted for a summer vacation that Roy spent with Dr. Mills exploring the Indian Serpent Mound in southern Ohio. Besides participating in the excavation of the specimens, he helped Dr. Mills prepare and display, in the museum, the products of their explorations.

Included among the friends at O.S.U. was no less than the President of the University, Dr. Wm. O. Thompson. Their friendship continued and Dr. Thompson paid a personal visit to Roy at the Henry Ford Hospital in 1917. A part of their

*The Roy D. McClure Lecture, presented May 23, 1961.

**Consultant, Department of Obstetrics and Gynecology.

conversation has often been repeated. In response to a request for his opinion about the general unrest at that time, President Thompson remarked that in his years as an educator it had been his opportunity to observe the growth and development of this group or that group, this sect or that sect, this faction or that faction, and to hear expressed a fear that one or another of these would spread out and overrun the state. He was not disturbed because every year the backbone of the country, the average American Citizen, came to the polls to cast his vote and thereby stabilized the situation.

Throughout the 4 years at Ohio State Roy maintained a high scholastic rating, and he received the degree of B.A. in 1904. The courses were chosen to comply with the entrance requirements of Johns Hopkins. Besides the scientific courses in biology, physics and chemistry, requirements included 2 years of Latin and a reading knowledge of French and German.

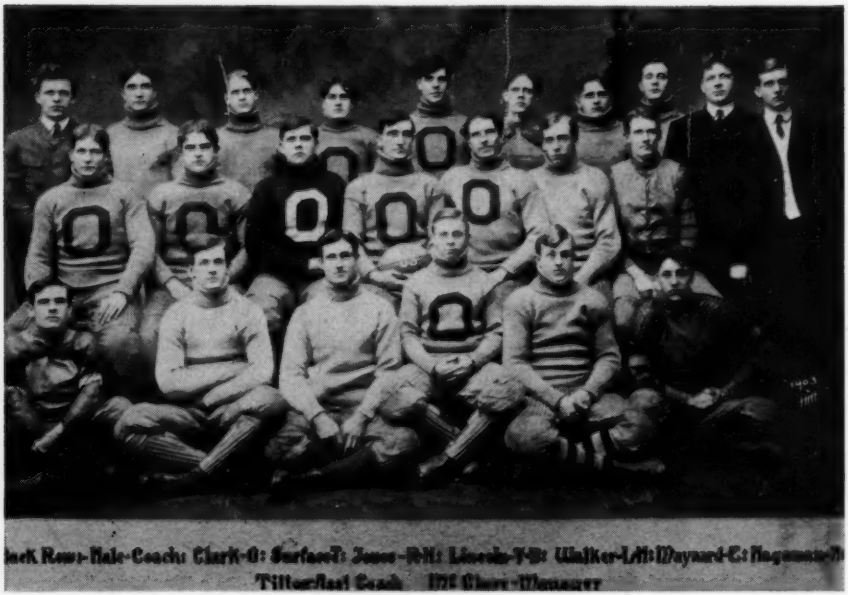


Figure 1

Ohio State University football team, 1903. Roy McClure on the extreme right was manager.

In 1903 he was manager of the football team (Fig. 1). He played varsity basketball in 1903 and 1904. In 1904 he was captain of the basketball team.

In the photograph (Fig. 2) George Bellows is shown at his right. One can see from the photographs that Bellows was physically strong. He was a superb ballplayer. His personal charm and accomplishments in Art endeared him to many Americans because his portrayal of America of his day was so realistic. His pictures are found in many museums and are a monument to him. Roy was always proud

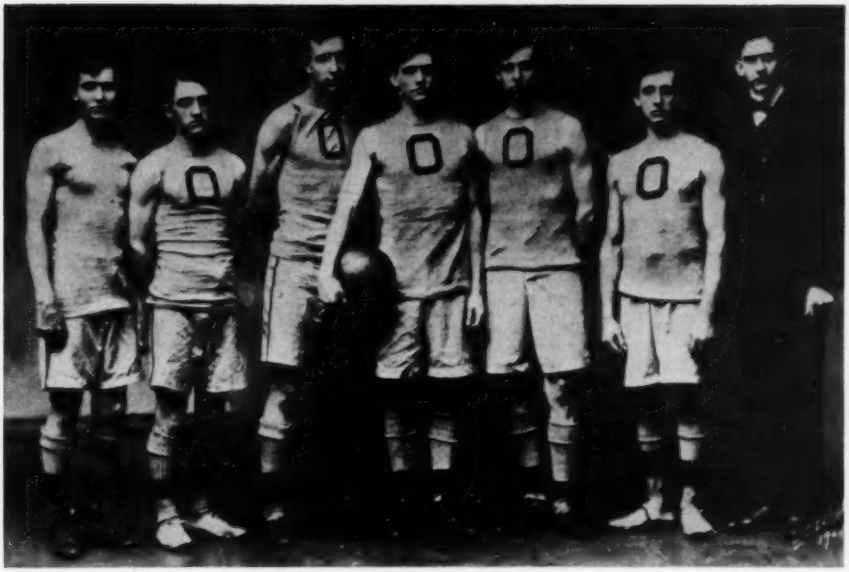


Figure 2

Roy playing center was captain of the O.S.U. basketball team, 1904.

of their friendship which came to an untimely end with the death of Bellows from appendicitis at age 43.

Roy received the honorary fraternity memberships in Phi Beta Kappa, Sigma Xi, and an honorary Doctor of Science in 1936. He was president of the Detroit Alumni Club of O.S.U. 1939 to 1942, and was national Alumni President 1925 to 1927. He was a member of the committee of 100 (alumni) who organized and launched the Ohio State Development Fund, and he had a hand in planning the University Research Foundation.

The photograph (Fig. 3) was taken when he was presiding at the annual business meeting of the Board of Directors meeting, and forum of the Alumni Association in 1926.

The selection of a medical school in 1904 was a very different problem than it is today. In general, medical education in the United States was at a low ebb. There were really less than a half dozen schools worthy of consideration by a serious student. The status of medical education was appreciated by Abraham Flexner who was assigned by the Carnegie Foundation for the advancement of Teaching to investigate the medical schools in this country. In 1907 he found 155 existing schools and suggested that the number should be reduced by 120. Actually it was reduced

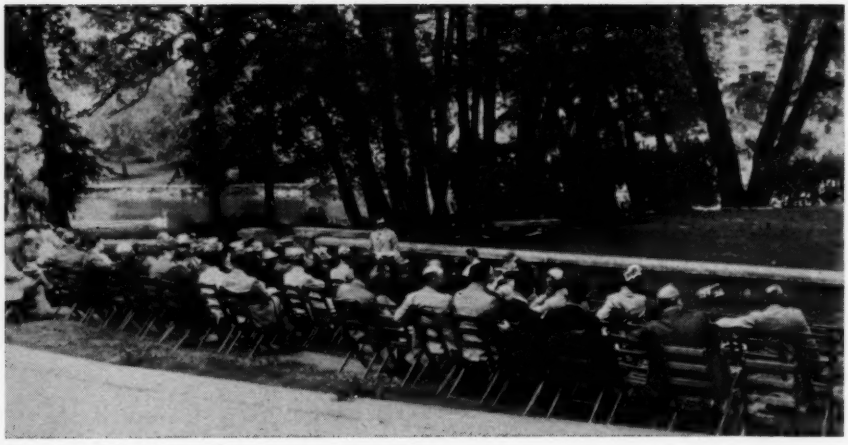


Figure 3

Roy, 1926, was presiding at the annual Board of Directors meeting of the Ohio State University Alumni Association. This is a distance shot, but he is on the platform and the only one facing the camera.

to less than 70. In his "Bulletin Number Four" he wrote;[1] "The schools were essentially private ventures, money making in spirit and object. A school that began in October would graduate a class next spring; it mattered not that the course of study was two or three years; immigration recruited a senior class at the start. Income was simply divided among the lecturers, who reaped a rich harvest. 'Chairs' were therefore valuable pieces of property, their prices varying with what was termed their 'reflex' — No applicant for instruction who could pay his fees or sign his note was turned down. The examinations, brief, oral, and secret plucked almost none at all: even at Harvard, a student for whom a majority of nine professors 'voted' was passed. The man who had settled his tuition bill was thus practically assured of his degree, whether he had regularly attended lectures or not. Accordingly, the business throve. Rivalry between different so-called medical centers was ludicrously bitter."

The Johns Hopkins Medical School graduated its first class in 1897. Thus was introduced a new model which embodied the best features of education in England, France and Germany adapted to American conditions. In retrospect it would seem that it would have been easy to choose the one best medical school, but the ideals of the Hopkins school were new and perhaps revolutionary. Then, too, there were solicitations by agents from the various schools in existence. Today the situation is different. There is no best medical school. One has a wide choice of good schools.

THE JOHNS HOPKINS MEDICAL SCHOOL

The spectacular success of the Johns Hopkins University and Hospital was not a mere accident. It was through the foresight and wisdom of a few men who were

the nucleus that the development of these institutions was completed. First of all, the founder, Johns Hopkins, amassed a fortune of seven million dollars which he regarded as a trust to be disposed of for the benefit of his fellow men. According to his instructions one half of the money was used for the university, and the other half was for a hospital. Six years before his death he personally selected the Board of Trustees who faithfully carried out his plans. In retrospect, it is apparent that Mr. Hopkins's fondest hopes and wishes were fulfilled and that for the "benefit of his fellowmen", education in general and medical education in particular were profoundly influenced.

In a letter of instructions to his trustees he wrote, — "In all your arrangements in relation to this hospital, you will bear constantly in mind that it is my wish and purpose that the institution should ultimately form a part of the medical school of that university for which I have made ample provision by my will." The close association between the hospital and medical school was unique and presented a new impetus to medical education.

Mr. Hopkins, in his letter of instructions to the trustees also wrote,[2] — "I have given you in your capacity of trustees, thirteen acres of land, situated in the city of Baltimore — upon which I desire you to erect a hospital." — "It is my wish that the plan — shall provide for a hospital which shall in construction and arrangement compare favorably with any other institution of like character in this country or in Europe. It will therefore be your duty to obtain the advice and assistance of those at home or abroad who have achieved the greatest success in the construction and management of hospitals". — "It will be your especial duty to secure for the service of the hospital, surgeons and physicians of the highest character and of the greatest skill."

The University, Medical School, and Hospital were established by the conscientious effort of many farsighted men. With due regard to the trustees and their advisers, it is apparent that the key man, second to the founder, was the first president of the University, Daniel C. Gilman. He already had experience as an administrator in other schools. He had studied educational methods abroad and was personally acquainted with many men and women who were prominent in teaching and research in Europe and at home. He knew when and where to seek advice. For his faculty he selected outstanding scholars and scientists and then he let them alone. The same policy was continued for the selection of heads of departments in the Medical School. For the first Dean he chose Dr. William H. Welch and time has demonstrated the wisdom of his choice. Dr. Welch was also Professor of Pathology with a special interest in research which he imparted to students as well as to other members of the medical faculty. Dr. William Osler was appointed Professor of Medicine and his contributions were different from those of Welch but no less important.

Dr. William H. Howell wrote[2] — "It may be said that the faculty of the medical school as first organized, its so-called Advisory Board, contained no dead wood. All of its members contributed in different ways and to varying degrees to the successful development of the School and Hospital, and to the promotion of

medical knowledge. It was extremely fortunate in having in its group two men, Welch and Osler who were blessed with a magnetic kind of personality that attracted and influenced all who came in contact with them. In almost any assemblage these men would have been selected as leaders, because of their ability and their personal force and charm. One such individual was enough to confer distinction upon a faculty. To have two at the same time was a gift of the Gods."

Welch and Osler, key men of the medical school, profoundly influenced medical education. It would be difficult to estimate their direct influence and impossible to comprehend their indirect influence through the faculty for whose selection they were largely responsible. Although time does not permit, it would be a pleasure to review the personalities and contributions of the brilliant galaxy of teachers. It is pertinent, however, to refer briefly to a few with whom Roy McClure came in closest contact. Among these few, Dr. Halsted comes first, because as student and resident in surgery Roy was associated with him for ten years. Furthermore Roy emulated the Professor.

Halsted's life was divided into two contrasting periods by his experimentation with, and innocent addiction to cocaine. At Yale he distinguished himself in athletics but not as a scholar. He was a model of muscular strength and vigor, full of enthusiasm and the joy of life. From the time he began the study of medicine he was devoted to his profession. He studied in Europe and was very much impressed with the European methods of teaching. Returning to New York his professional advancement was rapid. He was generally considered to be a bold, daring and original surgeon, an indefatigable worker, and an inspiring teacher.

Halsted was a pioneer in antiseptic surgery. He read all of Lister's papers and repeated his experiments on animals with a more thorough study of the results than would have been possible for Lister because of the development of bacteriology. Halsted cultured wounds treated by the use of Lister's methods and found bacteria on the surfaces. This prompted him to a careful microscopic study of wounds. He realized that care in operating, the exact approximation of surfaces and the avoidance of dead spaces was as important for results as the supposed avoidance of bacteria. Everything connected with surgical procedures he studied experimentally.

A new field of investigation was suggested by Koller's announcement in 1884 that with cocaine the conjunctiva and cornea could be anesthetized. Unaware of the habit forming quality of the drug, Halsted and his associates experimented extensively with it. The fortunate outcome of these experiments was the discovery of local anesthesia by injection. The dire consequences were the addiction and subsequent illness of the experimenters, unconscious as they were, of the menace. Although most of the victims succumbed, Halsted conquered it by superhuman strength and determination.

Although Halsted had strength of character to overcome the addiction to cocaine, his personality changed. Medical students and residents knew only the new personality. It is probable that none of them knew of his tragic experience. Dr. Welch knew, and had faith in his possibilities and was responsible for his appointment as Professor

of Surgery at Hopkins. This challenge and interest coming at that time were opportune as stabilizers, for Dr. Halsted often said that he found the greatest satisfaction of his life in the training of surgeons.

A description of Halsted's personality that would be satisfactory to all is not possible. However, Roy McClure approved of Harvey Cushing's characterization in his biography of Halsted.[3] — "A man of unique personality, shy, something of a recluse, fastidious in his tastes and in his friendships, an aristocrat in his breeding, scholarly in his habits, the victim for many years of indifferent health, he nevertheless was one of the few American surgeons who may be considered to have established a school of surgery comparable, in a sense, to the school of Billroth in Vienna.

He had few of the qualities supposed to accompany what the world regards as a successful surgeon. Overmodest about his work, indifferent to matters of priority, caring little for the gregarious gatherings of medical men, unassuming, having little interest in private practice, he spent his medical life avoiding patients — even students, when this was possible — and, when health permitted, working in clinic and laboratory at the solution of a succession of problems which aroused his interest. He had that rare form of imagination which sees problems, and the technical ability combined with persistence which enabled him to attack them with the promise of a successful issue. Many of his contributions, not only to his craft but to the science of medicine in general, were fundamental in character and of enduring importance."

At the opening of the hospital in 1889, Halstead entered a new phase of his life. During the interim after his affliction he was very close to Dr. Welch, who was an understanding friend and a wise cousellor. He came to live with Dr. Welch and worked diligently in his laboratory on basic problems of operations. He thought out a plan for a professor of surgery to follow: — 1. to perfect the technical methods of surgery; 2. to study experimentally the great topics which from the beginning had aroused his interest, and 3. to establish a school of surgery by long and thorough training of his assistants.

Halsted's devoted adherence to his plan was apparent to students and associates. The public appreciation was expressed by repeated reference to the "Halsted school of surgery" and the "Halsted era of surgery". Although his surgical discoveries and inventions were important, it was the training and inspiration of surgeons that built the monument which perpetuated his memory. Among the fortunate few who were selected for the long period of training Roy McClure was rewarded and, in turn, he was able to share later in the development of the Henry Ford Hospital.

At the very time, October 1904, that Roy entered the Hopkins Medical School a new operating room was formally opened, and this was to serve as the center of his activities for the next ten years. In honor of the occasion the staff assisted Dr. Halsted for the first operation in this room. Fig. (4). A copy of this photograph was available to the students and was cherished by them. The picture exemplifies some of the characteristics of surgery as practiced then. You will note the flat top table with no mechanical devices for adjustment of position. Sterile gowns were

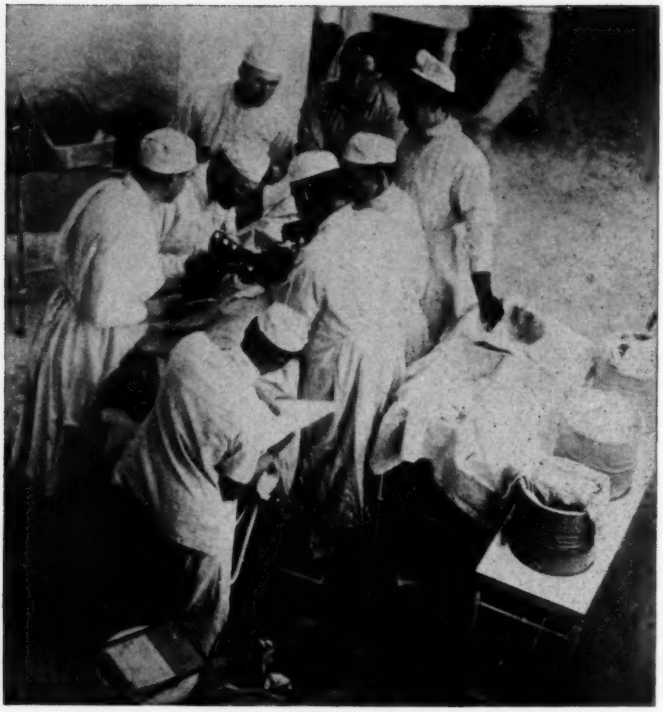


Figure 4

First operation in the new surgical ampitheater, 1904.

worn, also a small cap and rubber gloves but no face masks. The ether cone devised by Dr. Halsted was made of pasteboard covered with oiled silk and toweling. A sea sponge was tucked inside the cone to retain the ether. The preparation of the patient consisted of a thorough scrubbing with soap and water. The soap was removed with ether, then alcohol. Potassium permanganate solution was painted on the area, then the mahogany brown of this procedure was removed with oxalic acid. Finally the area was deluged with 1 : 1000 solution of bichloride of mercury. Although the instruments had been boiled for ten minutes they were kept immersed in a 1 : 30 solution of carbolic acid. When the instrument was to be used the solution was shaken off.

The operation was performed for osteomyelitis of the femur which was a subject of especial interest to the professor at that time. He was using his favorite mallet of fiber bound in metal. The team consisted of first assistant Dr. John Finney, second assistant Joseph Bloodgood, third assistant Harvey Cushing and instrument man Hugh Young. These valuable assistants pictured at the operation were important in the training program. Later Roy became very grateful for the friendship of each and every one of them.

EXPERIMENTAL SURGERY

Experimental surgery was an important part of the professors plan. While he was waiting for the hospital to open he spent his time in the laboratory. When the medical school opened he continued his own investigations and allowed some of the staff and students to work with him. An elective course in animal surgery was offered and soon became very popular. Later, much of the responsibility for the course was delegated to Harvey Cushing, (1901-1912). So far as possible the exercise was likened to the actual performance of surgery as conducted on a patient in the hospital. A group of five for each table consisted of an anesthetist, surgeon, two assistants and a family physician. Each week for five weeks the members of the team rotated so that each one had experience in all positions. A history was composed, an anesthetic chart recorded and an operative note written. Meticulous attention to detail was required. The whole procedure was carefully supervised. While this method was an excellent training in surgical technique it also permitted the instructors to see what students were adapted to experimental surgery. That Roy McClure qualified is shown by the publications which resulted from his work. He was especially interested in vascular surgery which brought him association and friendship with Alexis Carrel. His experimental work was continued by spending a year at the Rockefeller Institute with Carrel.

The basic principles of vascular surgery were well established by that time. Reliable methods for repairing and anastomosing blood vessels were well developed. Autologous, homologous and even heterologous transplants had been successful. Some progress had been noted in storage of transplants. Carrel had studied these problems for years. His method of anastomosis, reported in 1902, was widely used. Essentially, his method was the insertion of three traction sutures at equidistant points on the circumference of the vessel. Then a continuous stitch was inserted between each of the guide sutures. The method was as satisfactory clinically as it had been in animal experimentation.

TRANSPLANTATION OF KIDNEYS

At the time that Dr. McClure was working with Carrel, transplantation of the kidneys was a subject of great interest. Tissue transplantation, especially skin graft, was an accepted surgical procedure. However, the transplantation of a whole organ depended upon a means of connecting blood vessels. The development of satisfactory methods of vascular surgery by Carrel provided him with the essential feature for transplantation of organs. The idea of transplantation of organs attracted a number of investigators, and in 1902 Carrel and others reported the transplantation of kidneys into the neck of dogs. There were many failures due to technical difficulties, but there were instances of long survival of autotransplants. One of Carrel's dogs lived for more than 2 years after the autotransplantation of one kidney to the neck and later removal of the other kidney. The animal gave birth to two litters of puppies during this period, but later died from intestinal obstruction.

The experiments performed included transplants to the neck with anastomosis of the renal vessels to the carotid and jugular; transplantation to the groin with anastomosis

of the renal vessels to the femorals; transplantation within the abdomen with re-anastomosis of the vessels to the renals or anastomosis to the splenics or iliac vessels, or to the aorta. Homotransplants were tried with an average survival of about 16 days.

In 1907 Carrel worked out a method for mass transplantation in dogs and cats. Cats seemed to be more suitable for the procedure. He describes four stages in the transplantation en masse;[4] "(a) preparation of the kidneys; (Fig. 5); (b) perfusion and extirpation of the kidneys; (c) preparation of the host, (Fig. 6); and (d) graft of the kidneys into the abdomen of the host." (Fig. 7).

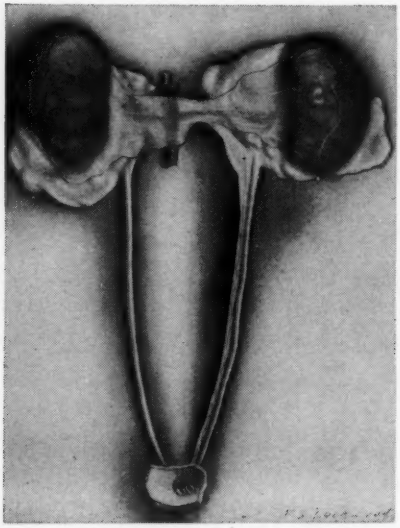


Figure 5

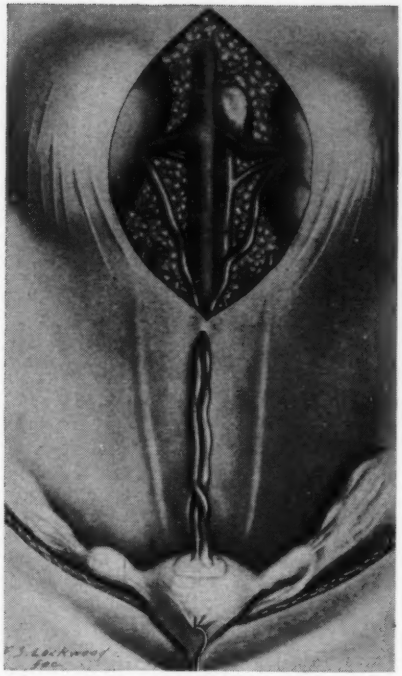
Preparation of the kidneys with ureters and their attachment to the bladder.

Figure 6

Preparation of the host.

He wrote that "It is evident that all resources of modern surgery must be used to prevent infection and shock after such an operation, which necessitates a large transverse incision of the abdominal wall, the evisceration of the intestines and spleen, a double nephrectomy, the stopping of the aortic and caval circulations, the section of the aorta and vena cava, and the opening of the bladder. The animal is handled and operated upon with the same rigid asepsis and care used for a human patient in a well-equipped hospital."

Fourteen experiments were performed, but five of the animals died almost immediately. The other nine were reported. In a footnote, Carrel writes that "Several of these operations were made with the aid of Mr. R. D. McClure of Johns Hopkins University, whom I wish to thank for his assistance." The designation "Mr." rather than "Dr." was used because it was another year before Roy was graduated. The experiments were reported in great detail. Roy was justly proud of one of these experiments because it was so successful, and secondly he reported it at the seventh International Zoological Congress. The photograph (Fig. 8) shows a very active



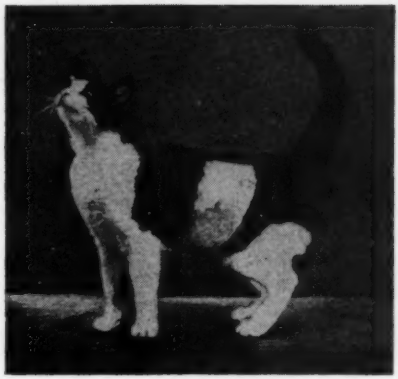


Figure 8
Roy's famous cat.

Figure 7
Transplantation of both kidneys complete. The blood vessels have been anastomosed. The patch of bladder, including ureteral insertion, has been attached.

animal on the twenty-first day after the operation. The death was from an organized hematoma pressing on the renal vessels.

The fundamental technique for the successful transplantation of kidneys was established. It paved the way for continued study of kidney function, which Roy watched with interest although he was occupied with other things. Had he lived a few years more, he would have seen the successful clinical homotransplantation of kidneys which was the ideal that prompted the early experiments.

HYDROCEPHALUS TREATED BY DRAINAGE INTO A VEIN OF THE NECK

At the suggestion of Alexis Carrel and Harvey Cushing experiments were performed on dogs in the Hunterian Laboratory. The purpose of the experiments was to establish a permanent drainage between the intracranial subdural space and the cervical venous system through the interposition of a transplanted blood vessel.

Six experiments were made upon normal dogs. A circular area of the skull was resected. Within this area a flap of dura was turned down and a circular hole about the size of the vessel to be transplanted was made in its center. The external jugular was then bared by continuing the incision over the lower part of the skull and down across the neck. The exposed jugular was then ligated distally and a bull dog clamp placed on its central end. The vessel was cut across and irrigated with salt solution.

The opposite jugular or a femoral was used for the transplant. The valves in these veins prevented the upward flow of blood. A vein was chosen with a bifurcation at one end (Fig. 9a) so this could be opened and a large flange could be made (Fig. 9b). The vein was drawn through the hole in the dura from the inside so that the flange came to lie against the inner surface of the dura. The flange was then stitched to the dura (Fig. 9c).

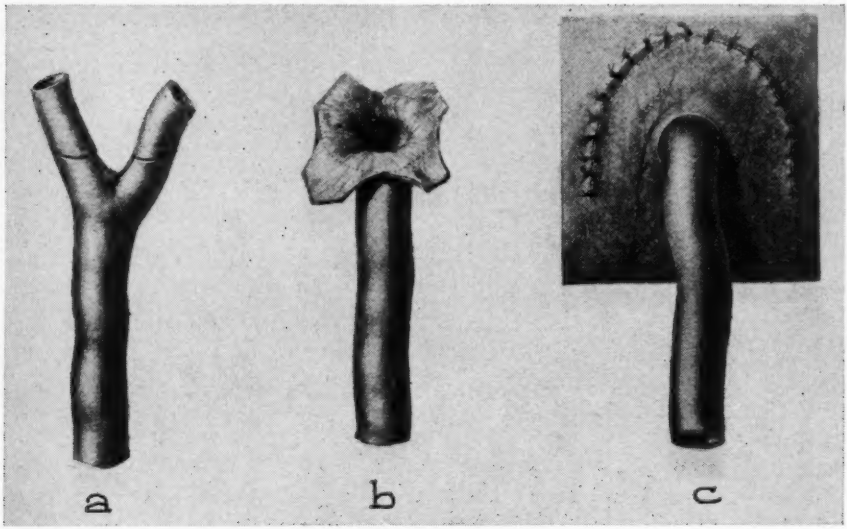


Figure 9

Vein transplanted in dura.

A straight intermuscular channel for the vessel was made by blunt dissection through the muscles to the exposed ends of the jugular vein. The transplanted vessel was drawn through the tunnel and sutured to the end of the divided jugular by the end-to-end method of Carrel.

Since the animal experiments were successful the procedure was tried on one of Dr. Cushing's patients. It was a ten month old baby who had shown, from the time of its premature birth, evidences of hydrocephalus, and during the three months previous to the final operation had undergone numerous attempts to relieve the pressure symptoms of the rapidly enlarging head. At various hands numerous punctures, ventricular and lumbar, had been made, with only temporary relief. Temporary relief had been obtained by a previous operation under the temporal lobe to open the bulging third ventricle. The temporary improvement was suddenly interrupted by a rapid refilling of the ventricles. Then tension became so great that on numerous occasions ventricular punctures were urgently necessitated in order to ward off what seemed to be threatened medullary paralysis from pressure.

"The operation was performed July 23, 1908.[5] It proved much more simple in accomplishment than had been the case with the canine experiments. Under cocaine

anaesthesia a portion of the cephalic vein was taken from the father's arm, including the bifurcation of the vessel at the elbow. This vessel was placed in protective vaseline as described in the laboratory experiments. Examination of the child had shown that in the lower portion of the external jugular on the right side there were two valves which prevented any expiratory regurgitation of blood into the external jugular, for the vein proximal to this point dilated markedly when the child cried, and in this part of the vessel could be seen an expiratory pulsation which did not pass above the valves. The condition seemed most favorable, therefore, for the transplantation, and the presence of these valves in the external jugular did not demand the transplantation of a vessel which should also possess them."

"The child stood the operation well, and the fontanelle remained soft, but a few hours later a sudden elevation of temperature occurred such as not uncommonly seen after operations, upon the central nervous system, particularly of infants, supposed in the absence of leucocytosis and with no wound infection to be due to some central thermic disturbance. This unlooked-for complication, which was followed by death shortly after, was the more unexpected, since the child had stood previous rapid withdrawals of fluid by punctures and the earlier and much more serious and extensive operation without any complication whatsoever."

"The report of these experiments and of this single operative experience with a clinical case is presented merely as a suggestion of what may possibly be accomplished by applying the methods of blood vessel anastomosis, which have been perfected by Alexis Carrel, to the establishment of drainage in suitable cases of idiopathic hydrocephalis."

During the past decade there has been a revival of interest in the problem of draining the fluid of hydrocephalus into some other structure. Satisfactory results have been obtained. Unfortunately these reports did not come in time for Dr. McClure to see them.

RESIDENCY

The attraction of experimental surgery influenced Roy's choice of postgraduate training. Because he was rated among the first twelve in his class he was eligible for internship at Hopkins. Instead of accepting this opportunity, he chose to go to New York where he was a voluntary assistant at the Rockefeller Institute with Carrel for a year. Then he served a year as resident at New York Hospital under Dr. Pool. His vacations during these years were pleasant and profitable interludes, because he had the satisfaction of being physician to the Jekyl Island Club.

The Club was located on Jekyl Island, which is just off the coast of Georgia. The membership included many of "the 400" of New York. Among the number were the Goulds, Pierpont Morgans, Pullitzers, Vails, Hills, Rockefellers, Vanderbilts, Whitneys, and many other celebrities of that time. He availed himself of the social and physical culture and acquired many valuable and lasting friendships. He frequently referred to those associations with pride and satisfaction. It was really a great event in his life.

Vascular surgery with its applications as in transplantation of organs and transfusions was the dominant interest during the year at Rockefeller. During the next two years clinical work was foremost, and with Dr. Pool practical application of vascular surgery enabled them to report twelve transfusions by direct anastomosis of artery to vein using the Carrel technique. Roy maintained an active interest in blood transfusion throughout his career.

BLOOD TRANSFUSION

Blood transfusion has now become so commonplace that one is apt to forget the slow evolution of the important historical events that makes the present day method of transfusion possible. Even in the earliest times the importance of blood in the animal economy was appreciated. Blood was regarded as synonymous with life and was thought by the ancients to be the seat of the soul. It was invested with mysterious properties and in medieval times was more closely related to magic than to medicine. For the medical profession the first really fundamental contribution was the publication by William Harvey in 1628 of his conception of the circulation of the blood.

Harvey's discovery opened new possibilities for transfusion. Many different experiments in animals were tried, injecting all sorts of fluids into the circulation and finally blood. Calves or lambs were the most common donors of blood. A large assortment of devices for the transfer of blood were reported. Many claims for priority were asserted. It was generally conceded that Lower of England was first in animal to animal transfusion and Denys of Paris was first for animal to man transfusion. Denys reported some remarkable successes but in 1668 one of his patients died following a third transfusion and the widow instituted proceedings against him. He lost the suit and soon the transfusions were banned in France and a similar silence prevailed in England throughout the Eighteenth Century.

The incompatibility of blood from different species of animals was gradually recognized and the use of animals blood to man was discontinued. Blundell, an English obstetrician was probably the first to record a successful transfusion with human blood in 1829. For postpartum hemorrhage he gave 8 ounces of blood by means of a brass syringe and cannula. Later he added a pump to facilitate the flow and still later used gravity for the driving force. Blundell also demonstrated that blood is not injured by passage through an instrument.

Aveling, another obstetrician, treated a postpartum hemorrhage by transfusion in 1872. His apparatus consisted of an india rubber tube to form an anastomosis between the donor and recipient veins and a little bulb in the middle to act as an auxilliary heart. He used silver tubes to insert into the veins. Various other investigators devised means of connecting donor to recipient by means of tubes.

Up to this time one of the main difficulties in transfusion was clotting of blood. To obviate the difficulty Braxton Hicks in 1869 used blood mixed with one fourth its volume of a solution of sodium phosphate. Unfortunately, all of his four patients died, perhaps from the chemicals used although transfusions were used only in

extremis. At least he conceived the possibility of a means of overcoming clotting. Defibrinated blood was used, but this procedure lost a valuable portion of the blood.

During the nineteenth century transfusion was used chiefly by obstetricians and usually as a last resource. The results were never very encouraging. Two problems were discouraging, (1) clotting of blood, (2) the number of severe reactions and even death that followed transfusions. In relief of the first problem, the development of vascular surgery became important.

Dr. McClure wrote an article on transfusion of blood in 1917 entitled "Transfusion of Blood.[4] History, Methods, Dangers, Preliminary Tests, Present Status. Report of one hundred and fifty transfusions." He wrote, "The next great steps were made in this country chiefly in the line of simplifying the technique and making more sure of success in transferring a sufficient quantity of blood from the donor to the recipient. The work of Carrel on the direct successful end-to-end suture of blood vessels (as well as the cannula devised by Crile), added a new interest."

"Carrel's success, as you know, was due mainly to the most rigid aseptic technique and the prevention of blood clotting in the wound, or in the several blood vessels during the operation, by means of careful hemostasis and saline irrigation. His manual dexterity, fine needles and suture materials and exact approximation of intima and media, were also important factors. Then came the Crile cannula with the principle of everting one vessel over a hollow cylinder and inserting this into the recipient vessel. In this method the intima coats are brought together and there are no raw surfaces. Following this there came a number of imitations with improvements, the best of these being the Elsberg cannula."

The main objection to all of these methods is that they cause a considerable amount of inconvenience to both donor and recipient. The amount of blood cannot be determined absolutely excepting, perhaps, by methods suggested by Libman and Ottenberg. Oftentimes the artery would go into a spasm from which it would not recover for half an hour or more, so that only a very small quantity of blood could pass through. This spasm sometimes could be overcome by irrigations of hot salt solution."

At the time Dr. McClure was a student intern and early residency, this direct method of transfusion was in vogue. Soon the method of injection by syringe was perfected, and the blood could be drawn in one room and taken to another for injection into the recipient. The syringe method was first described and used by von Ziemssen in 1892. In 1913 Lindeman reported an elaboration of the method of von Ziemssen.

"At the same time that work was being done to find a mechanical way of preventing clotting, that is, a more rapid or more perfect way of transferring the blood, investigators were turning their attention to the chemical side of the problem with the hope that if the blood could be kept from clotting by means of some chemical, the difficulty of transfusion would be immediately solved. The two chemicals most used have been herudin and sodium citrate."

The second problem of severe reactions and death from transfusions was largely explained by the work of Landsteiner. In 1900 Landsteiner divided human blood into three groups according to the iso-agglutinin content, and his pupils added a fourth in 1902. It was not until 1910 when Moss's paper gave wide publicity to grouping that blood transfusions began to be practiced with confidence. When Dr. McClure came to the Henry Ford Hospital the method of choice was use of syringe and citrated blood. The experience of World War I added impetus to the use of blood transfusions. Now immuno-hematology has become a specialty and the art of blood transfusion has become so complicated a procedure that only a few experts can understand all its ramifications.

By invitation of Dr. Halsted, Roy returned to Hopkins in 1912 to complete his residency. It was apparent from the beginning that Roy had great potentialities as a surgeon, and that his interests were akin to those of Dr. Halsted. They had confidence in each other.

Soon after his return to Baltimore he became ill with typhoid fever which was widespread in the city at that time. He asked me to arrange for a good special nurse. Fortunately I knew that Helen Troxell was available, and she fulfilled all the requirements. She accepted the assignment and that was the beginning of their romance. Four years later they were married.

The clinical material seen by Dr. McClure during his residency was quite different than what he saw in his later years. His illness with typhoid emphasizes the prevalence of infections at that time. Every summer many hospital beds were occupied by typhoid patients, thereby reducing the number of beds available for surgery. One of the serious complications of typhoid was perforation of the intestine. The number of perforations at Hopkins averaged about five a year. This complication offered a difficult problem for diagnosis and those patients were a poor surgical risk. These unfortunate victims provided material for learning and teaching surgical judgment. The incidence of malaria did not equal that of typhoid but it was often seen. While it was primarily a medical problem it also concerned the surgeon in the differential diagnosis of the cause of pre- or post-operative fever. Amebic dysentery and abscesses were relatively common. Management of these infections was only temporizing. The real solution of these problems of infection came through improvement in sanitation — an interesting chapter in medical history. The deformities of rickets provided surgical material. Osteotomies for the correction of bowlegs, knock knees and sabre shins were common procedures. On account of Dr. Halsted's special interest in problems there was an abundance of aneurysms, carcinoma of the breast and thyroids. Endocrinology and psychiatry were in their infancy. There was no insulin, B_{12}, sulfa drugs nor antibiotics. Tumors, benign and malignant, presented the same general types as are seen today, but they were larger and more of them were inoperable. Education of the public has brought a great change in the field of oncology.

The duties of surgical residency were demanding but rewarding. One could not be sure how he rated with the Professor, but to be chosen as a resident and

allowed to remain in that position indefinitely was the best evidence that he was liked. Roy was among the few who were favored with the privilege of eating luncheon in the Professor's office. Roy admired and emulated the Professor and unconsciously acquired some of his mannerisms. In addition, he enjoyed a fine friendship with other members of the surgical staff. It was not easy to leave Hopkins, but his regrets were softened by his marriage at that time, and by the challenge of a new undertaking at the Ford Hospital.

"EARLY DAYS AT THE HENRY FORD HOSPITAL"

About fifty years ago, a group of citizens of Detroit subscribed to a fund for the purpose of constructing a hospital, to be the Detroit General Hospital. Their plans incorporated good ideas gained from visits to many other hospitals. Their ambitions were realized for the buildings were considered to be up to date. When the staff was organized, Dr. Frank Sladen, who was the medical resident at Johns Hopkins, was invited to join them as chief of medicine. Fortunately he accepted and came to Detroit in 1913. While waiting for completion of the buildings he engaged in private practice in Detroit. Subscriptions to the hospital fund lagged and Mr. Henry Ford was induced to take over the hospital. He paid back the other contributors and the hospital became his property. The name of the institution was changed to the Henry Ford Hospital. Soon after that he was seated at dinner beside Dr. Will Mayo. Mr. Ford told him that he found himself with a hospital on his hands and asked what to do with it. The reply was to get a full time staff and leave the problem to them. Future events showed that the idea was acceptable.

In October, 1915, Dr. Sladen brought a few of his private patients to the hospital as a nucleus from which the number has continued to increase (Fig. 10).

Figure 10

The Henry Ford Hospital, 1915, situated on a 20 acre lot at the geographical center of the city. M-units, laboratory, service building and garage.

A few months later Dr. Janney Smith joined him on the medical staff. There were a number of surgical problems and Dr. McClure was invited to come as Surgeon-in-Chief. He came in the summer of 1916.

It was known that Mr. Ford felt that the rich and the poor received excellent medical care, but the great middle economic group was less fortunate. It was his desire that this hospital should provide good medical care for those who wished to pay but could not afford large fees for the service. Therefore, the prices were to be kept reasonable. There was no provision for charity, a word which was not mentioned in Mr. Ford's presence. However, a great many people who were without funds at the time they needed medical attention were given the best of care and at a later date were given an opportunity to work to pay for the services rendered. Another stipulation of Mr. Ford was that patients should be seen by appointment because he disliked to see a long group of waiters on the bench. While Mr. Ford left the medical policies in the hands of the physicians, one of his representatives sometimes made suggestions. Having in mind the assembly line methods he suggested that they do tonsillectomies on Monday, appendectomies on Tuesday, fractures on Wednesday. He also suggested that there should be no autopsies performed, nor any smallpox vaccine be given at this hospital.

After Dr. McClure came to Detroit it was only two years until the hospital was closed on acount of World War I. During that time the surgical staff consisted of enough men for an operating team and one extra for general utility. The buildings completed at that time were the M-Units with a forty-nine bed capacity, the operating room, laboratory, service and maintenance building and the garage. The four story building which now contains the A,B,F,H and I units was under construction (Fig. 11).

Figure 11
Photograph of architects plan, 1917.

When the shell was completed without any division into rooms, it was leased to the U.S. Government for one dollar a year.

Soon after the M-Units were opened the beds filled. The growth of the clinic was assured. It was apparent that more room would be needed to accommodate the expansion. Besides caring for patients, the staff served as a consulting board for examination of possible rejects from the draft. The war spirit enticed one after another of the staff until too few remained to operate the hospital properly (Fig. 12). The hospital was closed in the summer of 1918, and all who could pass the physical examination entered the service. Dr. McClure was commissioned a major.

Figure 12

Photograph taken 1940 of personnel before war, still in the employ of the hospital. Besides the nurses and doctors are Miss Bateman and Brevick from File and Record. In the back row, Bill Mahan and Alex Croft from Maintenance.

Through a tacit understanding the surgical staff was to form the nucleus of an evacuation hospital staff. On induction we were sent to various camps but soon were assigned to Camp Shelby in Mississippi. There the staff of evacuation hospital 33 was collected and we were led to believe that we would be ordered overseas shortly, as that had been our request on induction.

The organization of the staff was complete, but still no orders to go overseas. By a little sleuthing it was learned that a colonel in camp was conniving to be assigned to command our unit. Thereupon, Major McClure wrote a letter explaining the situation and posted it outside the camp to avoid military channels. The letter reached his friend in Washington and in a few days we were off to Hoboken. On November 10, 1918, we boarded the Sierra which was a ship that had been retired before the war and had just been reconditioned after having a rudder shot off.

The next day, November 11, we heard the great celebration in New York on account of the signing of the armistice. No shore leaves permitted. The news of the armistice aroused hope that the war was all over and that our overseas trip would be cancelled. All doubt was removed when on the next day we sailed in a convoy under strict regulations because the submarines could not yet have been notified to cease activity. It was a rough trip and ninety per cent of the men on board were sea sick. Our destination was Bordeaux. As we sailed up the River Gironde the French children shouted from the banks "La guerre est fini." That was not news because we had already heard about the armistice before we left New York.

After debarkation at Bordeaux, the personnel of "33" were quartered nearby in the town Salle-Boeuf. The population of this town was about 80. It was Major McClure's and my good fortune to have a small up-stairs room in the home of the village blacksmith. According to the social customs, the blacksmith rated high on the scale. In that room were two beds, one chair and a smoking fireplace. If we could tolerate the smoke, we could keep warm. If the smoke was too bad then we could withstand the cold. Through the one window we could watch the ceremony of shoeing an ox, which took place just across the street. With the gesticulations of four men and the activity of the blacksmith, the ox was properly shod. One day we heard a great commotion in the yard back of the house. Upon investigation it was found that the family and neighbors were gathered around a well from which they had just pulled up a drowned dog. Needless-to-say we obtained our drinking water elsewhere after that. During the short time we remained in Salle-Boeuf we learned many interesting things about rural life in France.

Even though the war was over, the chief function of the evacuation hospital was continued, that is to move. The longest stay we had was in Vichy where again the Major and I were favored with exceptional quarters, for we had the privilege of a room in the building that had formerly been the German embassy. This was quite elegant with a private bath. During the time spent in France, Major McClure was intimately associated with Major Evarts Graham who was in command of another evacuation hospital. This proved to be a lasting friendship which endured many years after returning to this country. From November, 1918 to May 1919 we sojurned in France. The return to the States was on board the Alfonso XIII which was just newly equipped for U.S. service but retained the Spanish crew. The pleasant voyage home compensated for the rough exit in November. On arrival in New York we immediately traveled to Camp Dodge in Iowa and the unit was disbanded, and the medical officers discharged.

The condition of the Ford Hospital was the main interest when we returned to Detroit. The shell of the building was occupied by the army. Since there were no partitions on any of the floors, each unit served as a large ward with cots up and down the length of the room. The quarters seemed to be highly satisfactory to the occupants, for it was quite difficult to dislodge them. It was apparent that it was going to be many weeks before the buildings would be vacated. During that time, Dr. McClure invited me to join him in a tour of New England, which was partly

for investigation of hospitals and medical centers, but largely for pleasure. On that trip the second-hand automobile sometimes faltered. The motor sputtered, hesitated, stopped in some out of the way place. In his characteristic quiet manner Roy heaved a sigh and said "Human life is not so simple." That incident with those words expressed his placid philosophy.

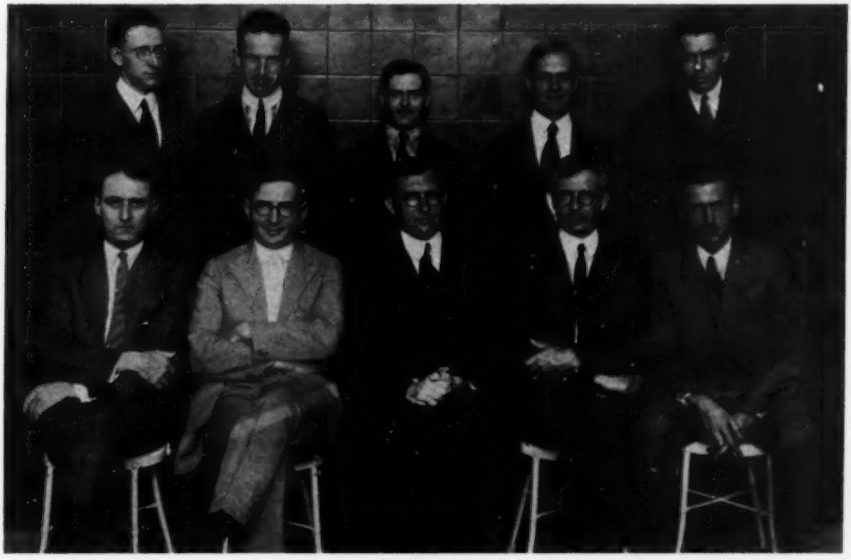


Figure 13
Surgical Staff, 1922.

The M units were reopened November 4, 1919, just a year after the armistice. The former staff returned with enthusiasm for the opportunity to reorganize the clinic. The first new patient was number 5426 continuing the system of records previously used. It was not long until surgery was again interrupted because there was a serious influenza epidemic in Detroit. All available beds were occupied by medical patients and operations were limited to emergencies. Gradually a normal balance was restored and a steady growth of the clinic proceeded continuing even today.

As soon as the military personnel withdrew, construction of the rooms in the new building began. Enough rooms were completed so that the first patient was admitted December 1, 1921. The staff was still small (Fig. 13) but adequate. Gradually the units were equipped and the rooms were occupied as soon as they were ready. The increasing number of patients necessitated an increase in the staff (Fig. 14 and 15). Specialties were developed in the departments of surgery and medicine.

As Surgeon-in-Chief, Dr. McClure was now launched in his life's work from which there were to be no more interruptions. He accepted his responsibilities as administrator. His clinical interest never lagged. Through his ability to gain friends

Figure 14
Surgical Staff, 1923.

Figure 15
Medical Staff, 1925.

he performed a valuable service in public relations for the hospital and for medicine. A specific instance was his fine relation with Henry Ford Sr. which enabled him to interest Mr. Ford in many medical projects. His surgical achievements have been presented in previous addresses.

Roy McClure was a naturally reserved and dignified person whose charming personality attracted a host of friends. He instinctively cultivated certain friendships with true prediction of their worth. These friendships in turn rewarded him and those with whom he was associated. It was fortunate that Roy studied medicine at the time that there was a revolution in medical education and that he was able to carry on the spirit of his teachers. These annual memorials are a fitting tribute to a dedicated physician.

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ALLERGY TO LEECHES*

THOS. J. HELDT, M.D.

The purpose of this contribution is to ring the bell of caution in the field of medicine to the end that the bite of the leech must be included in the disconcerting and even dangerous reactions to other insects,[1] such as mosquitoes, spiders, bees,[2,4] wasps,[3] hornets,[2,5] ants,[6] and the lowly snail.[7] In the mind of most lay people and in the mind of most doctors in fact, the medicinal leech is without blame and can be incriminated with difficulty, but it has been vulnerable throughout the centuries and its bite is not to be taken too lightly at the present time. However, the medicinal leech is one thing; the wild leech is quite another. It is very particularly the latter upon which the writer will center his attention with pertinent references to the former.

The leech is a parasite of the animal kingdom. A glance at the following Classification Table gives its usual taxonomy.

In general, it may be well to think of the leeches as falling into three groups: marine leeches, fresh water leeches, and terrestrial leeches. It is of course with the fresh water leeches that we are here concerned but a few words regarding the other two kinds will not be amiss. The marine leeches are quite secure in their salt-water habitat and feed largely on fishes. The terrestrial leeches have made history and gained recognition in divers ways. Sir J. E. Tennent[19] gives account of how the land leeches routed an entire battalion of English soldiers from their wooded encampment in Ceylon. Hammerton[20] also refers to this incident in his discussion of the "Pigmy Trappers," and further mentions these leeches have surprised and slain sleeping human beings. Harmer and Shipley[12] record how a genus of the fresh-water leeches, the Limnatis, proved disconcerting to Napoleon's soldiers at the Nile in 1798.

CLASSIFICATION TABLE*

Phylum Annelida
Class Hirudinea
Order 1. Rhynchobdellida (No jaws, but proboscis; colorless blood).
Family 1. Ichthyobdellidae (Fish leeches, mostly marine).
Family 2. Glossiphonidae (Fresh water leeches).
Genus Glossiphonia:
Glossiphonia stagnalis
Glossiphonia fusca
Glossiphonia complanata
Genus Placobdella:
Placobdella montifera
Placobdella parasitica
Placobdella rugosa
Order 2. Gnathobdellidae (With jaws, no proboscis, red blood, fresh water and terrestrial species.
Family 1. Hirudinidae (Three toothed jaws, 5 pairs of eyes).
Includes Hirudo medicinalis and the horse leech (Haemopis mormatis (Aulastomum gulo).
Family 2. Herpobdellidae (With three muscular ridges in place of jaws; three pairs of eyes).
Genus Haemadipsa includes a number of pugnacious land leeches with notorious histories.
Genus Limnatis proved a nuisance to Napoleon's soldiers at the Nile.
Genus Trocheta is an English land leech that lives on earthworms.

*For confirmations, variations, and amplifications see Selected References, 8 to 18.

*From Division of Neurology and Psychiatry. This investigative study was decided upon in July 1944. Request was made to the Research Committee of the Hospital and it was authorized as research project number 66. World War II responsibilities with personal health problems brought some protracted interruptions.

Fresh water leeches are common to the lakes, ponds, and creeks of the United States. Land leeches are less common but are well known to zoological gardens and most students of biology. When opportunity presents leeches feed avidly on the blood of vertebrates. Most leeches and especially the medicinal leech can ingest three times their own weight of blood. Since it requires from 9 to 12 months to digest such a repast meals may be few and far between. Leeches usually reproduce two times, during spring and summer. They are hermaphroditic, but the eggs of one parasite are fertilized by the spermatozoa of another leech. Leeches are of course of various sizes, from the barely visible horse hair size to several inches in length. The writer personally collected from the domesticated water buffalo of the marshes of the Marejo Island in the delta of the Amazon River a leech 6 inches in length and distended to 3 inches in width by the ingested blood.

A considerable literature has built up on the subject of leeches, both ancient and modern and in most languages. Hence, the bibliography for this article will be divided into Selected References and Supplementary References, to give better opportunity for checking and for verification. Extent of review will be judged on pertinence to the subject under discussion.

Drescher and Engel[21] in 1947 present a noteworthy article on the medicinal leech in the Netherlands. After historical references and comments they outline the use of the medicinal leech in their homeland. They list 44 references in their bibliography, but inasmuch as they concern mostly the pharmaceutical aspects of the subject they will not here be inspected further.

It is judged that Albach[22] in presenting his doctoral dissertation entitled: "Observations on the Therapeutic Use of Leeches with Particular Reflections as to Anaphylactic Appearances" made his primary consideration the determination as to leeches having a favorable effect on thromboses or thrombophlebitis. A secondary purpose is to note if anaphylactic reactions occur in the use of the medical leech.

In making his historical review Albach calls attention to some interesting data, including the following: Although blood-letting and cupping in all manner of ways were in common use by the Egyptians 3,000 years, B.C., and although used freely by Hippocrates (460-377 B.C.) and Erasistratus (300-250 B.C.) it was Nicander of Colophon (200-130 B.C.) who first used the leech medicinally. After him they were used freely by many: Themison of Laodicea (123-43 B.C., pupil of the great Asclepiades); Aretaeus of Cappadocia (30-90 A.D.); Galen (130-200 A.D.), and others. Antyllos,[23] notable Greek physician and surgeon (100-150 A.D.) was the first to use the leech-cut ("Blutegelschnitt"). If it be necessary to use leeches, and in case few are available, or a sparing number have been applied, it may prove expedient, at the time the leech has drunk his fill, to cut off his tail with a scissors (". . . den Schwanz mit der Schere Abschneiden"). After the blood has run out of the leech it will reattach itself and will not let go until it is removed by sprinkling some salt, soda, or ashes upon it. This observed fact is in use to this very day.

During the 19th century leeching in France reached an immeasurable degree, even to the extent that 100,000 leeches were used in one year in a single hospital. (". . . an einer einzigen Krankenhaus Abteilung wurden bespielsweise jährlich 100,000 Stuck gebraucht;"). This popularity was in large part due to lectures by Francois Joseph Victor Broussais (1772-1830), so much so that his promoted methods were referred to as Broussaisism. Heinz Bottenberg at the time declared: Upon such enthusiastic excesses a repercussion must of necessity follow ("Auf so wilde Uebertreibungen musste notwendigerweise ein Rückschlag erfolgen".) Such spirited use of leeching received its setback over the ensuing years. Rokitansky in Vienna and Virchow in Berlin were developing more and more disbelief in the humoral theory, and this discredit had a dampening effect on blood-letting, cupping, and the use of leeches.

Albach (p. 7) says the best known and most widely distributed leech species are: Hirudo medicinalis, the German leech; Hirudo officinalis, the Hungarian leech; and Hirudo Sanguisuga, the horse leech. The habitat of H. medicinalis he gives as all of Europe, southwestern Asia, and north Africa; that of H. officinalis as southern Europe, Yugoslavia, Hungary, and Bulgaria. He further says that since the mad days of Broussaisism H. officinalis has been used almost exclusively in medical practice; the horse leech, since it elaborates no hirudin, is not used medically. Albach gives credit to "John H. Haycraft" (John Berry Haycraft 1857-1922),[24] physiologist of Birmingham, England, for first isolating hirudin from the throat glands of the leech in 1884. After further declaring: "Der heute allein therapeutisch gebrauchte Blutegel ist der Hirudo officinalis" Albach describes the external colorings and markings of that parasite but he does not give those details necessary correctly to place that insect taxonomically. With references to different authors Albach records some general observations and anatomical details. Among them the following are of interest here: The life span of the leech is 10 to 20 years; it is not sexually mature until its 9th year; and, it must be 3 or 4 years old before it can be used therapeutically. The hirudin producing glands were discovered by Brandt in 1833.

Leeches are very sensitive to atmospheric conditions especially hot days and thunder showers. Albach (pp. 10-11) presents various methods used in applying leeches and encouraging prompt biting; the duration of attachment varies from 10 minutes to two hours depending on the sucking intensity and the temperament of the insect; it will fall off when it has obtained its fill; and, for some 24 hours there may be some bleeding where it was attached. He mentions that Dinand and Bottenberg had advanced studies to show that the leech could harbor a "leech-bacillus." However, investigations in the laboratories of the Hygienic Institute of the City University (Frankfort am Main), under the direction of Dr. Küster, did not confirm such findings, but instead showed that the ingested staphylococcus and the colon bacillus could live in the gut of the leech for months without noticeably disturbing its welfare. Albach (pp. 12-15) outlines with noteworthy comments the research studies of several investigators as to the pre-and post-operative use of leeches, and of parenteral injections of hirudin, in the hope of preventing or altering the formation of thrombi and emboli. Bleeding time and coagulability of blood is given due

consideration as are urinary excretion and changes. It is noted incidentally that the secretions of one leech can prevent in vitro the coagulation of 50-100 cc. of blood; on that basis the application of 60 leeches to a person at the same time could prevent the coagulation of his entire blood mass if that be estimated at 6,000 cc.

Albach cites (p. 17) Bosc and Delecenne[25] and Haupstein[26] as claiming that immunizing bodies are produced by the leucocytes of the patient in leech-therapy; and, Heisler that the application of 6 leeches in the course of 7 or 8 or more days can induce anaphylactic reactions. He firmly declares he disagrees in both instances.

Albach (pp. 18-19) briefly reviews two cases which to me have ear-marks of allergy to leeches. The symptomatology after the second application of the leeches is highly suggestive, but Albach made no immediate control studies, nor investigative comparisons, nor follow-up observations. Comparative injections of hirudin are carefully described, but concluding observation is voiced in this statement: "Eine Anaphylaxie oder etwas Aehnliches konnte von mir nicht festgestellt werden" (p. 21). (I could not confirm an anaphylaxis or a similar condition.) In support of this conclusion Albach records 16 case reports in the use of leeches for various conditions, varying from priapism to "cold abscess." (pp. 21-25).

He maintains that allergic and anaphylactic reactions to leech bite are merely local tissue responses. This for the reason that antigen-antibody elaboration to leech bite has not been proved. These deductions are clearly set forth in the 4th, 5th, 6th, and 7th statements of his summary:

"4. Infektionen durch Blutegel-Bisse sind möglich, aber offenbar selten. Meist handelt es sich um Erysipeloide. Diese dürfen nicht mit urticariösen Eczem oder anaphlaktischer Erscheinung verwechselt werden." (Infections due to leech bite are possible but obviously rare. They are involved mostly in the erysipeloids. These conditions are not to be confused wth urticarial eczema or with anaphylactic appearances.)

"5. Anaphylaktische Erscheinungen können auf Grund von Versuchen an 50 Fällen nicht bestätigt werden, weder beim Blutegel-Bis noch bei wiederholter intracutaner Impfung mit Hirudin." (Anaphylactic reactions, on the basis of investigative studies on 50 cases, have not been confirmed, neither by leech-bite nor by repeated intracutaneous injections of hirudin.)

"6. Rötungen, die bei beiden Applikationsarten gesehen wurden, sind nur lokale Reizungen der Vasomatoren-Endigungen mechanischer oder chemischer Art." (Erythemias, which may be seen with both methods of application, are only local irritations of vasomotor terminations of mechanical or chemical nature.)

"7. Die Antigen-Natur des Hirudin oder des Mundsekretes ist noch nicht erwiesen, deshalb mus vorläufig die Annahme einer Bildung von Immunkörpern und die Fähigkeit zur Auslösung anaphylaktischer Reaktionen abgelehnt werden." (The antigen nature of hirudin or of the oral secretions of the leech have not yet been

proved, therefore the assumption of the formation of immune bodies and the capacity to release anaphylactic reactions must be regarded as premature.)*

Sabrazès[27] opens his article with the statement: "I — Il est rare quon signale l'intolerance aux application de sangsues" (p. 642). Then he makes brief reference to the ancient use of the leech in India, Greece, and Rome with mention that its use was especially recommended by the School of Salerno. He says leeching was particularly promulgated by Nigrisoli's publication in 1665; more recently the studies of Derheims, Moquin-Tandon, Ebrard, and Busquet. Sabrazès then informatively reviews the work of Louis Vayson, with whom he seems very much in accord, except that he declares Vayson is in error when he states that the developing leeches of the Gironde aspirate blood from the engorged bodies of adult leeches, whereas the young leeches actually obtain their sustenance from frogs, tadpoles, and fishes.

Sabrazès remarks that at the time of his writing, 1933, that the average number of leeches sold per month by an important pharmacy in Bordeaux was from 30 to 100 at one franc 25 to one franc 50 per leech.

In "II" Sabrazès tries to answer these questions: "Y-a-t-i-l des cas de sensibilisation, des cas d'intolerance a l'egard des piqures de sangsues? Leur emploi risque—t-il d'etre limite per cette evenualite?" (p. 644). He gives two case reports at some length. One of them, to my mind, is indicative of allergy to the leech bite (p. 644); and of it he remarks: "Ce cas releve probablement d'un etat de sensibilisation, sinon d'anaphylaxis." (p. 645).

In his "III," Sabrazès outlines the obtaining of hirudin from the heads of leeches; its use in thromboses and various diseases, and with appropriate comments and interpretations.

His discussion of "IV" opens with: "Les accidents du fait de l'application de sangsues sont rares. Il y a plus d'un siecle, Paul Jolly (Sur quelques accidents qui peuvent resulten de l'application des sangsues, Nouvelle bibliotheque medicale tomes III et IV Paris, 1827) leur consacrait un travail." Then with brief references to authors Pelletier and Hazard, Derheims, and Mayer as to the probability of septic material carried to the patient in the bite of the leech, he remarks: "Il est donc indispensable d'examiner les sangsues et d'ecarter les douteuses." He adds that except for the reaction of hypersensitivity he knows of no other risks in leeching beyond the foregoing then the tendency to lipothymie of some nervous patients and an occasional excessively prolonged bleeding after the leech has fallen off. Sabrazès concludes his article with this statement: "L'etude des sangsues est a nouveau d'actualite et souleve toujours des questions de biologie dont nous venons de laisser entrevoir l'interest." (p. 647). (The study of leeches is a new question of the hour which ever raises inquiries of biology which bring a welcome challenge to our interest.)

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*In the closing statement of his article (p. 26) Albach remarks: "Meine hierüber (regarding details of hirudin effects after detachment of leech) zum Beweise angestellten Arbeiten and Versuche werde ich in einigen Wochen veröffentlichen." However, although eight subsequently published articles by Albach have been found, the title of not a one reflects any further study on leeching.

Jimenez, Miguel F.,[28] was much concerned in the first half of the 19th century about "accidents" his patients experienced in the application of leeches. He reported these "accidents" at some length. Outstanding is an urticarial reaction of considerable severity. He mentions two deaths resulting from this type of accident. Jimenez states these urticarial attacks, often with syncope, always came immediately on termination of the leech having obtained his fill of the patient's blood.

Jimenez judged that the causes of these occasional reactions of his patients to leeches could be included under two general headings: First, the type and activities of the leeches themselves; secondly, the health conditions found in the persons to whom the leeches were applied. Under the first heading he included the species of leech, time of year in which the leech was used, whether the leech had been used on a patient before and whether these leeches inoculated the patient with some poisonous principle at the time of the bite. Under the second heading the class of disease or condition being combatted, regions of the body to which the leech was applied, and lastly the constitution, predisposition, or particular idiosyncrasies of the patient. Jimenez discusses each factor in turn. As to the species of leech he says only the gray or medicinal leech (Sanguisuga medicinalis) was used. He recounts how this type of leech was applied to three patients simultaneously from the same container. One patient developed urticaria, the other two showed no unusual reactions. He remarks that he is certain from his observations in every month of the year that time of year is not a factor in causation. He further comments that the re-use of the leeches does not seem to be a factor for such re-use is common in some of the hospitals, yet there is no increase in the number of untoward reactions reported. As to the inoculation of a poisonous substance at the time of the bite, he declares that he can only associate it with the particular status of the patient and not with the annelid.

Jimenez cites 15 different disease conditions for the 18 cases he reports and firmly concludes that it is not the disease which is the determining factor in the urticaria and the cerebral congestion encountered. He says further that he has never seen urticaria due to the application of leeches in patients with high fever such as in scarlatina and like conditions, although leeches were often used in such cases. He further concludes that the particular area of the body to which the leech is applied is also not a causal factor.

In referring to the cause of this recurrent accident, after leeches have been applied a second time to the susceptible patient, "to constitution, predisposition, or idiosyncrasies of the individual," Jimenez says: "It is with a feeling of advancing a subterfuge," but he adds: "It is very probable that this conception embodies the cause or one of the true causes of the repetitive morbidity." He likens the condition experienced by the patient to the occasional effect seen in the eating of "clams, crabs, etc." He makes a further point in saying that he has never seen this "accident" affect children under the age of eight, although leeches were applied frequently in order to avoid phlebotomy.

Jimenez, Lauro Maria,[29] a niece of Miguel F. Jimenez, apparently stimulated by the earlier observations of her uncle, made painstaking studies of the leeches

of the lower half of the Valley of Mexico. She investigated specifically those leeches which were at the time being used medically. She studied three species in particular. These species were collected from the streams and canals within a 100 mile radius of Mexico City. She describes fully and gives drawings of four species, but only three of these were consistently used in medical applications. Except for one species, to avoid confusion, she named the species according to the province in which the leech was collected. Glossiphonia granulosa was the leech most commonly used and apparently most collected. It was also found to be the chief offender. Hirudo Tehuacanea and Hirudo Queretaro she says were both thoroughly innocuous so far as precipitating morbid accidents. She briefly identifies Bdella Ixmiquiltanea as she does the genus Aulastoma but these are passing references only. In her article Lauro Jimenez gives credit to "a clever pharmacist of this city" (Herrara) for suggesting that the Glossiphonia granulosa secretes a poisonous substance which is injected at the time of its bite. Jimenez judges that the poison secreted by gland cells associated with the proboscis is minimal in effect when the leech has been cleanly kept. She adds that she has not been able to demonstrate any actual gland in dissection of the mouth of the leech.

Jimenez (L. M.) sums up her annotations in the following:

"1. Three species of medicinal leeches have been studied best in Mexico: the Glossiphonia granulosa, the Hirudo Tehuacanea and the Queretanea.

"2. The accidents which have been observed as a consequence of the application of leeches have been brought about by the Glossiphonia granulosa which appears to carry a buccal gland which secretes a poisonous liquid.

"3. The leeches of this species generally do not produce such accidents when they have lived for some time in clean water which is frequently changed.

"4. Furthermore, a special constitution in the patient is necessary for the reaction, a matter not known until now.

"5. The accidents consist of an urticaria more or less general, congestive attacks in the head, and swooning attacks which are sometimes fatal.

"6. The bites of the Queretaro and the Tehuacan are completely innocuous.

"7. These species extract a quantity proportional to their number: a little more than half a dram for each of them.

"8. In view of the terrible accidents produced by the Glossiphonia and the inoffensive bites of the Tehuacan and the Queretaro, it is not only useful but essential that there be acclimatization of the latter in this capital (Mexico City).

"9. And considering one of the causes which opposes this intention, the manner in which they reproduce, it is convenient to remove this, by providing the animals with the proper places where they can deposit their progeny, i.e., in adequate tanks."

In September 1866 Jimenez (L. M.)[30] reported: "Another Poisoning by Glossiphonia." She outlines the reactions of her patient, a woman 33 years of age, in

adequate manner. She concludes: "One recognizes that she was under the influence of poisoning caused by the Glossiphonia. But in this case, what could be the determining factor in the dangerous accident? It was not a bad quality which the leeches had acquired, from a poor condition of the waters in which they lived, because they had been placed and guarded with great care; neither could this be a predisposition or an individual condition of the patient, because in other cases, she had had no trouble from the use of the same kind of leeches."

"It is necessary to search in another part for the explanation of the phenomenon. It will be remembered that it is not strange that other animals used as food, acquire poisonous properties during the days in which they are occupied with reproduction. It seems to me that it is not an unreasonable idea to admit that this was the cause in this case. In fact, I remember on the same day the solicitude with which these leeches cared for their numerous progeny, sheltered under the abdomen."

"Maybe in the moment of fecundation, there is produced in this animal a toxin which is absorbed by the same wound which is made by the stylet which it has in its mouth; the pathological accidents produced by some of the mollusks, without heads, do not admit of another origin. They are produced when the embryo leaves the egg, they fix themselves under the branchial region and appear to be there naturally. The shell-fish eaten in that state causes eruptions of urticaria with swelling of the face, and sometimes suffocation and other nervous symptoms."

Jimenez, L. M., in the details of her article refers to the studies of Mendoza, Gumesindo and Herrara, Alfonso.[31] These professors of pharmacy open their article with the following statement: "Clinical experience has demonstrated a fact which science has not yet resolved, namely, the urticaria produced by the bite of the leech which is used here." They then refer to article by M. F. Jimenez in 1844. They recount in clearcut manner the symptoms recorded by Jimenez. These authors declare: ". . . the annelid used in this capital, at least in our time, is not of the genus Hirudo de L. Sanguissuga de Savigny or Jatrobdella de Blainville, which is the only kind used in Europe, but it is of the genus Blossibdella de Blainville, or Glossiphonia of Moquin Tandon. They promptly call attention to, ". . . a difference in the structure of the mouths of these two genuses, which distinguishes the tribes; the Hirudo has three mandibles armed with small teeth, similar to those of a saw and the Glossiphonia lacking these mandibles, and instead has a small tube with a long, fine bristle, like a sound or fine trocar. Thus, the first provides for suction by scarification by the mandibles, while the second makes a perforation by introducing the natural trocar deeply into the dermis, in a manner similar to that of the mosquito (culex pipiens) whose tube is similar but not the same as that of the Glossiphonia . . ." Then follows a comparison of the inflammatory wheals produced in keeping with the size of the two insects. The "clear liquid" secreted in the mouths of both facilitates the punctures made and is a further factor in the untoward reactions of some persons. The authors quote Blainville, ". . . speaking of the accidents which take place in Europe from the bite of the medical leech, 'It is necessary to believe that the inflammation occasionally produced by the bite of the leech depends on

the difficulty which the animal has in biting — and perhaps also in the mucous material more or less altered, held in the buccal disc and introduced into the wound.' " "Mendoza and Herrara then emphasize the following:

"There is something which has been well proven, according to the reports which we have seen from the practitioners, namely, that the use of the Glossiphonia some time after its removal from the original water source only rarely produces the phenomenon in question. This leads us to believe that the liquid introduced into the wound is more irritating because of the kind of food which the leech has in its natural state; it is well known that this has a great influence on the secretions of an animal; furthermore, it is a fact that our leeches live in swampy places; it has also been proved that the more swampy the natural habitat, the more poisonous the buccal secretion; when the annelids are kept in a barbershop, the nature of the waters is changed, i.e., previously they were in contact with animal materials and vegetables in decomposition, but now they are in contact with clean and edible things. One must take into consideration the frequency of the change of water and its effect on the diminution of the burning quality of the buccal secretion. The clam (Mytilus Edulis), although in a distinct manner, produces phenomena very similar to those which originate from the Glossiphonia when one does not take the precaution of washing it repeatedly before eating it. To all this, the following objection could be raised: What is the reason that all persons to whom the annelid is applied do not experience the symptoms which are the object of this investigation? We believe it could be answered that here we have the idiosyncrasies, temperament and nature of the disease, the age of the person, and the place of application which we would call predisposing causes; then it is a fact well explored that even the bite of the mosquito, which we have taken as the point of comparison, does not have the same effect in various persons, although the poisonous liquid has been introduced by the bite into each individual. The same observation has been made with respect to the accidents originating from the ingestion of clams. Gervais says 'We believe that the intoxication with these animals is in some cases the result of an individual predisposition.' "

Some of the deductions of Mendoza and Herrara are given in the followings language:

"1. The Glossiphonia has a liquid or buccal secretion of more irritating quality when less time has elapsed since it was captured, and when the place of its habitation has been more swampy.

"2. The secretion is less poisonous when the time of captivity has been greater and when the number of washings has been greater.

"3. The accidents produced are in relation to what we have called predisposing causes."

Then with the caution: To avoid the use of "recently caught" leeches; and, the suggestion: that the "genus Hirudo" be used ". . . in place of the Glossiphonia,

which for some cause produces such alarming symptoms and even death at times," — the authors close their contribution with this further deduction:

'In conclusion, we shall state that the indicated phenomena would by chance call the attention of the European naturalists, so much so that some of them believe

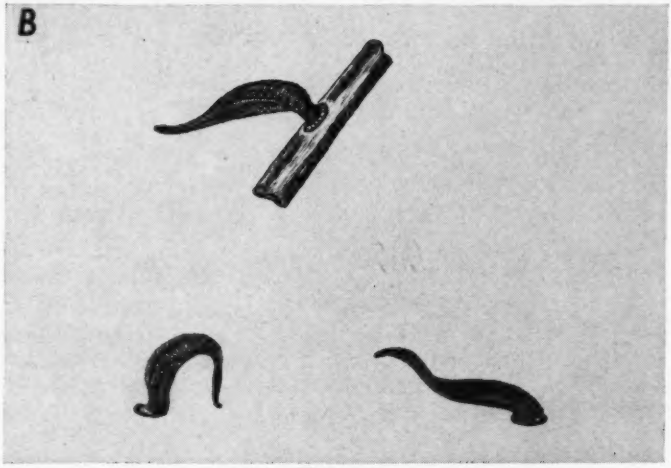

Figure 1
A. Lake Pleasant, Lapeer Country, Michigan
B. Glossiphonia fuscea x1/3

it is impossible that the genus Glossiphonia could serve as a leech for the extraction of blood; and in proof of this assertion, we see such as was expressed by Fremond in his excellent monograph on medicinal leeches: 'Some authors have written that the black leech, the common leech, and the humble leech are used indiscriminately. It is an error to be refuted: the black leech, not being other than the Aulostama vorax, the common, the nephelis octoculata, the deprunida, a glossiphonia, it is entirely impossible that they could be used, since they are not able to pierce the skin of a man.' Against this observation, we present the simple authentic fact (as amply presented in the foregoing), and with proof so disagreeable that it even involves death itself."*

Paulet[32] in 1808 reports a case, that of an adult woman to whom 6 leeches were applied, 3 to each arm. Apparently one of the leeches very directly punctured a communicating artery between the "cubital and radial arteries," and forthwith a considerable hemorrhage of arterial blood was at hand. The arresting measures common at the time were to no avail. The bleeding was so free and excessive that real disquietude was aroused in both patient and the doctor. Paulet finally stopped the flow of blood effectively by placing his thumbs on each side of the puncture wound. He sums up his observations as follows: "1. That leeches may sometimes puncture an artery or a vein." "2. That in the use of this type of insect it is important to assure one's self that there is not some artery projecting into the area where it is planned to make the application, which is really easily determined by the presence or absence of arterial pulsation." "3. That the compression of an arterial vessel with the fingers, when it is practical, is the means, not only very gently but also most prompt and the most certain in a case such as here reported; and, that an hour of such compression accompanied by calm and confidence is thoroughly sufficient to produce the desired effect."

Stuart[33] in 1805 introduces his, "Observations on the Occasional Injurious Effects of Leeches," with this statement: "Physicians observing the bites of leeches to be occasionally followed by troublesome inflammation, ulceration, and gangrene, have attributed these to some venomous quality of the insect. But, as the precautions founded on this opinion, have proved ineffectual in obviating the evils noted, the opinion may be justly suspected to be fallacious."

He then describes three species of leeches common in his area (Pa., N. Y., N. J.) at that time without designating them by name, but he adds: ". . . the large brown leech is the species most generally employed in medicine." After a general review of the functioning of this leech he further states: "I attribute them (injurious effects upon the patient) to the state of the system, or to that of the particular patient to which the leeches are attached. . . . because the effects mentioned never occur, except in such cases as evidence the presence of a morbid diathesis, general or local, in the patient to which they are applied; and, because they frequently

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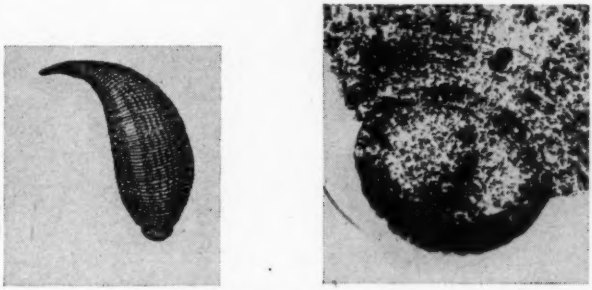
*I am very much indebted to Conrad R. Lam, Chief Surgeon in Division of Thoracic Surgery in the Henry Ford Hospital for the translation into English of the 4 Spanish articles listed under numbers: 28, 29, 30, and 31, in the Selected References.

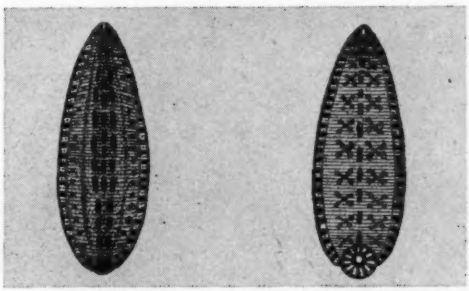
do occur where such diathesis exists." Stating "I have seen many," he reports a case in point, — that of an adult male to whom leeches had been applied to an inflamed perineum. After explanatory details Stuart concludes: ". . . that bad consequences are to be apprehended from leeches when applied in an inflammatory diathesis before general bleedings have been performed; in a general gangrenous diathesis; in an extremely irritable habit; and last, when applied to a patient actually affected with inflammation, ulceration and gangrene."

Telo and Panciroli[34] report two cases of local hypersensitivity to Hirudo officinalis. Appended to their article is the following summary in English.

"Two rare cases of abnormal cutaneous reactions to medical blood leech are presented in this article.



Anterior sucker, enlarged, showing pit from which proboscis is projected.



Ventral View Dorsal View

Glossiphonia fusca

Figure 2

"The first regards a subject with obvious signs of an allergic diathesis, who was afflicted with an asthma of mixed etiology, in the multiple sensitized phase, and in whom the first bite of the medical leech, gave rise to no abnormal reactions, but in whom the second bite (10 days later) caused local reactions in the form

of a swollen erythema, a severe pruritus of the histamine type, and an eosinophilia in the blood.

"In the light of these facts, the successful therapy with synthetic antihistamines, and the rapid cutaneous reactions which follow the injection of a protein extract of the leech, appear to substantiate the etiopathogenetic hypothesis of the AA, concerning an acquired hyperergy to Hirudo officinalis.

"The second case on the other hand reacted to the first bite of the leech with a large hemorrhagic pruriginous halo in the hepatic area at the point of the bite. This manifestation was insensible to the action of antihistamines, of slow resolution, and not accompanied by ematological changes.

"The etiopathogenesis of the manifestations seen in the second case, is pictured in the light of their hypothesis, as one in the vast field of idiosyncrasy, with a particularly strong capillary toxicity due to acquired miopragic factors."

Heisler[35] in his chapter entitled: "Blutegel" (pp. 1236-1238) reports two seriously septic cases. He confidently describes the effective use of leeches in the recovery of these patients obviously experiencing generalized septicemia, when other measures of therapy had failed. He also briefly outlines three additional cases of patients experiencing anaphylactic reactions.

Orszagh and Alfoldy[36] report the preparation of "a coagulative serum prepared by injecting hirudin into animals." This article is cited to show that leeches are currently inviting considerable attention.

Shope[37] of the Rockefeller Institute of Medical Research published January 17, 1957 in the Journal of Experimental Medicine a very thought provoking article entitled: "The Leech as a Potential Virus Reservoir." In telling manner it outlines the technique used in injecting leeches with two different viruses, and records (p. 381): "The preservation of hog cholera virus in the bloody gut contents of leeches for as long as 3 months and the similar preservation of myxoma virus for as long as 5 months suggests that the viruses are well protected from physical and chemical factors that might be operative in the open. This relatively long period of survival conceivably could be of importance as a mechanism for the preservation of viral agents in matter, despite the fact that virus seems not to multiply in the leech, and that the leech serves only as a mechanical reservoir."

Additional sidelights on leeches are not difficult to unearth. However, it is judged that the foregoing are sufficient to underscore the warning found in the introductory paragraph.

* * * * *

A Case Report: A highly dynamic, sociable married man of 34 was admitted to the Dermatological Service of the Hospital at 10 p.m. on July 9, 1944. He was disturbed and somewhat fussy about some skin lesions just above his left ankle. He declared that they were painful and disconcerting because "They seem to make me

Figure 3

Left ankle showing old scar of former leech bite, and two lesions of recent leech bites.

feel miserable all over." Staff members of the Division of Dermatology apparently told him that the lesions were due to poison ivy and a solution of gentian violet was applied during the morning of July 10th.

Since the author had known the man and his family personally for some five or six years he paid the patient a friendly visit. At the time of that visit the patient was somewhat upset and declared: "The doctors tell me this is poison ivy, but you know there isn't any poison ivy within a mile of where I got this." (What did you get?) "Leech bites — two of them. I pulled both of them off and killed them with a stone and this is the second time leeches have done this to me." (Tell me.) "Back in July 1936 I was organizing a market for the Kroger people at Owosso, Michigan. I was there a couple of weeks, so on Sunday afternoon I went to the Genesee or Shiawassee River for bass. I didn't have any waders so I just hopped into the water in my shorts. Somewhat later I spied a leech on my left ankle — that's the scar there now. I pulled it off. The next morning about 10 or 12 hours after I had pulled the leech off there was a great deal of swelling and I went to a doctor in Flint. That doctor and my superintendent at the time thought that probably in my work I had bruised my ankle with a splinter of pork bone. It took eight days for me to get over it and here I am with a leech bite a second time. If you look at those places carefully on my left ankle, although it's hard to see with all that violet paint on, you can see where the two leeches had their suckers attached." Inspection really did reveal telltale markings which were evident even a few days later and more so after much of the gentian violet was removed.

The writer solicitously presented the complaints of the patient to Dr. Frank R. Menagh, physician in charge of Division of Dermatology. The doctor listened at-

tentively and thoughtfully, — then remarked: I've never heard of it, much less seen it. Looks like poison ivy to me."*

The skin lesions came under control and permitted the patient to be discharged on July 14th. During the time of his stay in the Hospital the writer further revewed his findings with the chief of the Division of Dermatology. The dermatologist was reluctant to consider leeches the cause of the lesions in question. However, the patient remained vehemently positive in his declarations to the writer. Accordingly, the latter undertook a bit of research in behalf of the problem. The lesions such as remained were photographed. (Fig. 3).

Next, it was undertaken to identify the leeches in question. Hence, the writer accompanied the patient to the area where the leeches lived** and he was successful in catching three of them. (Figs. 1 and 2) He used these as specimens and had them identified and classified and then sent them to the laboratory for the making of extracts which might be used as injection material. After some time the injection material was ready and the patient submitted to an intracutaneous injection of the material in his forearm, together with an injection of normal saline as a control. The writer, as a control, had similar injections. To these injections the patient had a positive reaction to the leech extract whereas the writer had no reaction. This test was in no way convincing to the dermatologist. Hence, the writer after some weeks obtained some hirudin from a commercial firm in New York City. Tests were again carried out. The patient showed a positive reaction to the hirudin but the writer, as a control, showed no reaction.

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*Such a sincere remark of 17 years ago is not uncommon even today. A letter to the American Medical Association contained this comment in the reply: "Although an allergic response from a leech is theoretically possible it is not likely to be common. Leeching is still being used in many areas and among many peoples, particularly among some foreign populations. It is certainly not a necessary nor recommended medical procedure." An inquiry to the U. S. Department of Health, Education, and Welfare brought in its reply this remark from the National Institute of Allergy and Infectious Diseases: "In regard to your question concerning the use of *Hirudo medicinalis*, I do not know of any place in the United States in which it is being used for medicinal purposes." In wonderment the author telephoned the Health Commissioner of Detroit and forthwith was given four verified addresses where living medical leeches can be obtained. The writer proceeded to one of the addresses and readily procured the dispensable leech. (V. C. Piaskowski Drugs, 7542 Michigan Avenue, at Florida, Detroit, Michigan). Mr. Slezak, the pharmacist, had a lively stock of leeches. "These are the Hirudo officinalis imported from Spain, 'They have no teeth.'" (Have call for them?) "Oh yes, the doctor upstairs prescribes them frequently and then there are other doctors." (names three additional doctors). Inspection of the anterior sucker of the procured leech clearly showed the distal end of its proboscis in the pit from which the proboscis is protruded, — no teeth seen.

About 10 years ago, a patient came from one of the suburbs of Detroit to the Eye Department of the Henry Ford Hospital to have a clinically applied medical leech removed from one of his orbital areas. Its harmless removal occasioned considerable concern at that time. Should it be desired to remove a leech before it has drunk its fill, it is easily done with a sprinkle of salt or soda upon it; blowing tobacco smoke upon it, or, touching it lightly with the burning end of a cigarette.

**Lake Pleasant, Lapeer County, Michigan. (See Fig. 1)

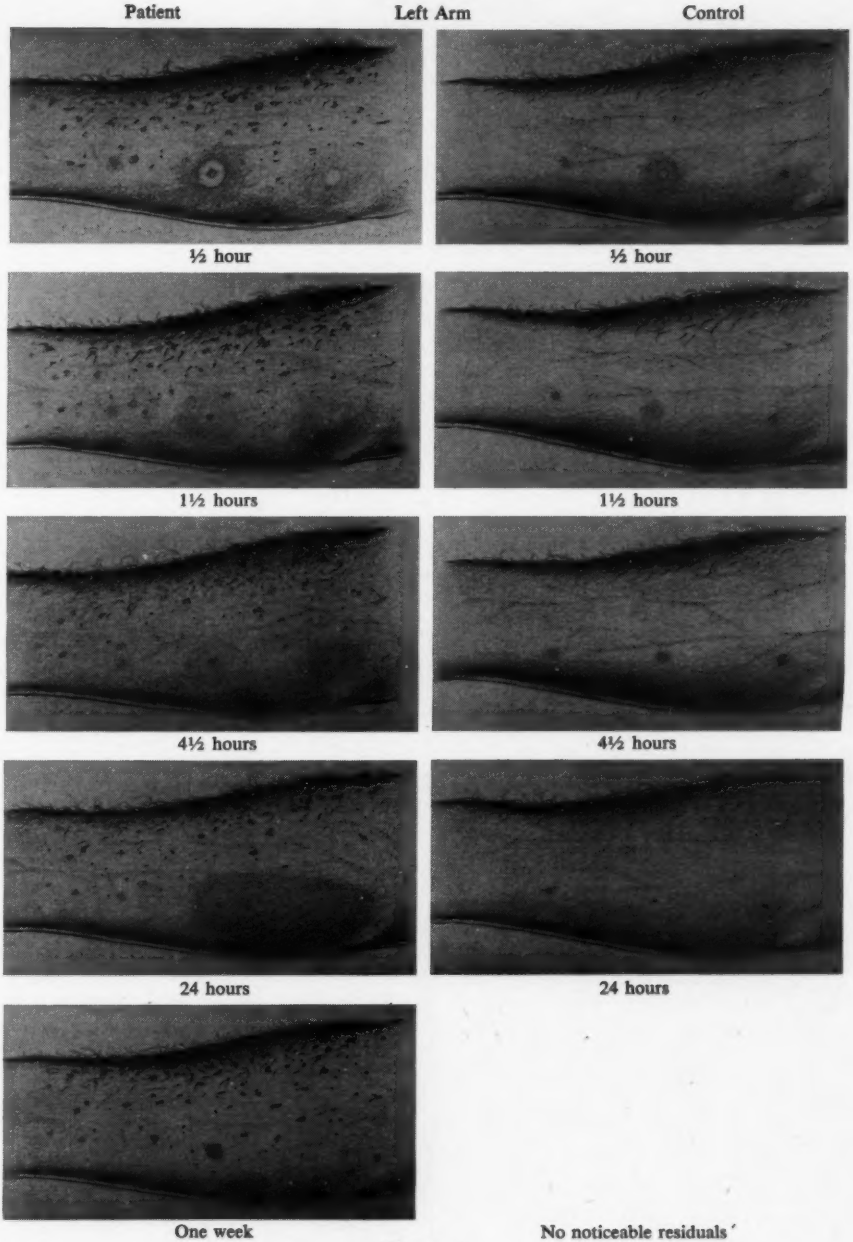

Figure 4

Reactions to intracutaneous injections of normal saline (0.025 ml., 0.9%); leech extract (0.25 ml., 1:10,000); hirudin (0.25 ml., 1:1,000,000); from left to right.

It was then planned to try the extraction material again but the dermatologist judged that it would not be dependable because: "First of all — you are two different types of person. The patient is a high type freckled redhead and you are more of stoic German disposition. His skin is more sensitive, yours more resistant. The only thing to do is to find a control who is more like the patient." A young redheaded interne finally volunteered. Intracutaneous tests were made. (Fig. 4) "That's not proof enough" said the dermatologist. So next, leeches again had to be obtained and it was not until August of 1946 that the author succeeded in persauding the very reluctant patient to submit to the leeches again and to help him obtain the leeches. However, the leeches were obtained from the original locale, four of them, and two of them were finally applied to the left forearm of the patient on August 24, 1946, under the supervision of the dermatologist; a third to the left forearm of the interne volunteer; the fourth to the left forearm of the writer. Observations were carefully checked by both the dermatologist and the writer and accurately recorded.* The patient responded with active reactions and required seven days of thoughful therapeutic attention. (Fig. 5) Reactions of the controls were negative. Also, the author had no reaction to leech bites in the tropical waters of the Amazon in 1958. Both the dermatologist and the writer were convinced that the patient did possess an allergy to the leeches in question, namely, the Glossiphonia fusca (Figs. 1 and 2) The Placobdella rugosa was found in the same waters as the G. fusca and it is judged that it too must be held under suspicion.

The dermatologist recorded his observations and interpretations in the hospital record of the patient as follows:

"This note is placed in the history at the request of Dr. Heldt giving our opinion of the reactions which occurred when the leeches were recently placed on the left forearm of this patient. The two leeches engorged themselves and dropped off spontaneously. This patient was observed during the period when these leeches were in place. It was found then and immediately after their removal that he had a perfectly typical wheal, such as would occur in an individual who was allergic to the material to which he was contacted. The reaction showed a wheal about 2½ cm. in diameter and this, in turn, was surrounded by a large areola. Following this, during the next 24 hours and to a less extent in the succeeding 3 or 4 days this patient showed a very vigorous reaction in this forearm. The arm swelled greatly, was hard and brawny and the patient had a typical febrile reaction.

"Our opinion as to the type of reaction here is as follows: this patient was definitely allergic, and the initial reactions were those of an individual who was

*Two leeches were applied and attached themselves to the left forearm of the patient at 3:45 in the afternoon of August 24, 1946. At 4:15 the leeches had taken their fill and fell off. Post-detachment bleeding after one leech stopped at 4:50; after the other at 7:10 p.m. A well marked wheal was present at the site of attachment by the time the leeches had obtained their capacity. Elevation of temperature was minimal throughout the seven days; pulse, however, was 110 for much of that time. WBC on August 26th, 27th, and 31st were between 10,050 and 10,750, PMN 76 to 57, PME 1-2, Lymphocytes 23-42; Hgb and RBC well within average. Fifty-one hours after detachment of the leeches swelling of the patient's left arm was very noticeable. It measured four inches more at left elbow than at the right.

allergic to the protein material which was absorbed through the epithelium and the traumatized areas as a result of the presence of the leeches on the skin. Whether this was only anti-coagulant or whether there was other protein material due to the presence of the leeches, it is of course, impossible to say. However, associated with this vigorous reaction, there was also an invasion of the lymph channels by bacteria, giving rise to an acute but short-lived lymphangitis which was responsible for the fever.

"This is not an unknown sequence of events. It occurs frequently around the face, particularly the cheeks, ears, eyes, and lips. The portal of entry here is usually an injury or fissure somewhere around the face, and there are other complicating features such as migraine, Bell's palsy, etc. in some of these patients. All of these, we feel, are part of the allergic response to the invasion of the lymph channels by infected organisms. In these cases when this recurs a number of times, the swelling frequently becomes permanent and in this instance, it has been diagnosed as an elephantiasis nostras dura which is due to the invasion of the causal organism."

The important and mutual deduction of the observing physicians then is, that the patient is allergic to leeches and the controls are not.

In conclusion, since many of the fresh-water lakes, streams, and ponds of the United States are populated with leeches, and since terrestrial leeches inhabit some of its wet lands, the medical profession and its unitary constituents must beware of the deleterious potentialities of the parasite leech *now* and *in the future.*

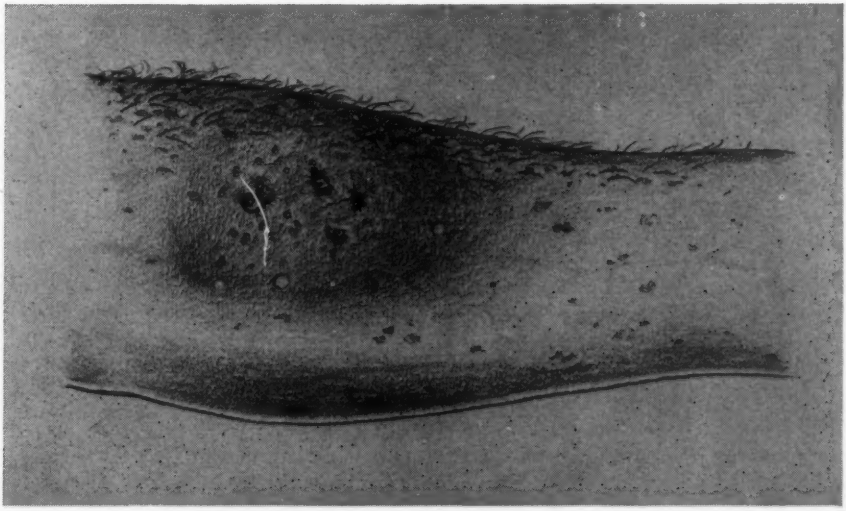

Figure 5

Reaction of patient; left arm, to two leech bites at 48 hours.

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STANDING WAVE PROBLEMS IN ACOUSTIC BEHAVIORAL TESTING OF ANIMALS

H. VAN DEN ENDE, E.E. (Delft)*

Introduction

Two audiometric testing rooms are presently in use, for acoustic behavioral testing of animals, at the Otological Research Laboratory. Acoustic stimuli consisting of pure tones are introduced by means of loudspeakers.

Speaking of rooms for pure tone audiometry, Beranek[1] remarks, "When audiometers which employ earphones are used, it is usually sufficient to keep ambient noise at a low level, without regard to the nature of the interior of the room. If a loudspeaker is used, however, the interior of the room becomes extremely important, since the presence of sound-reflecting surfaces will materially affect the nature of the sound that reaches the listener's ear. In particular, the level of the sound will vary from point to point in the room, giving rise to "dead spots" and "loud spots". In a companion paper[2] we reported sound pressure level patterns obtained in one of our rooms by means of a microphone traveling in vertical paths. The speaker was thereby driven with a signal of constant frequency and constant amplitude. The pressure from one point to another differed by as much as 30 db. at each of the commonly used test frequencies 250, 1,000, 4,000 and 16,000 c/s. The four walls and ceiling of this testing room were constructed of 4 inch thick acoustic panels, the sound absorption coefficients of which are listed in Table I as specified by the manufacturer.

SOUND ABSORPTION COEFFICIENTS OF WALL & CEILING MATERIAL

Freg. in cps	250	1,000	4,000	16,000
Abs. coefficient	0.99	0.99	0.83	**n.s.

Table I

This absorption was not obtained at the floor of the room which was covered with wall to wall carpeting, at a window in one of the walls, or at the margins of the panels. It seems surprising that the above results are compatible with such high absorption coefficients, but less so when it is realized that an absorption coefficient of 0.99 means a pressure amplitude of reflection of 0.1 of the incident sound.

The pattern of loud spots and dead spots shifts with frequency. This means that at a stationary point of observation the sound pressure level will change when the frequency of the driving signal is changed. This condition is undesirable in experiments designed to determine frequency discrimination abilities of animals.

For such experiments the ideal placement of the animal would be in an area where the walls do not reflect sound energy at all. Such an area can be obtained almost perfectly by the installation of wedges[3,5,6,7] and other structures on the walls.[4] The amplitude reflection coefficient then decreases with increasing frequency over a wide range. The frequency at which the amplitude reflection coefficient assumes the

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**Not specified

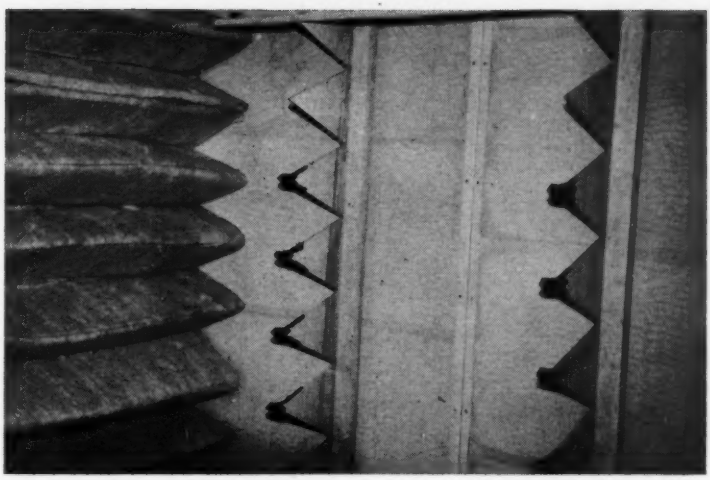

Figure 1

Figure 2

value 0.1 is called "cut-off frequency". Such a room is then called anechoic (that is without echo) for frequencies above the cut-off frequency. To render our existing facilities (the audiometric testing rooms measure 10 x 10 x 6½ ft.) anechoic for frequencies above 250 cps would require the installation of wedges with a wedge height of one foot. Such an addition was prohibitive because of the cost (estimated total cost per room $3,000). Cut-off frequencies lower than 250 cps would require

wedge height in excess of one foot which would not be practical. As an experiment, a less costly acoustical treatment was installed in the existing facilities in an attempt to render the room as anechoic as possible for frequencies above 250 cps.

Installation of Acoustic Material

One roll of a flexible, blanket type fiberglas, "Aerocor", 72 inches wide and 100 foot long was acquired. The sound absorption properties of this material are indicated in Table II.

SOUND ABSORPTION COEFFICIENT OF "AEROCOR"

Aerocor Blanket Material
(Owens Corning PF — 399)
Thickness: 1 inch
Density 2 pcf*

Frequency cps	125	250	500	1,000	2,000	4,000
Absorption Coefficient	0.10	0.51	0.63	0.94	0.91	0.89

*pcf = pounds per cube foot.

Table II

Studs 2 by 1½ inches were erected 1½ inches from the existing walls without defacing the walls with screws, see Fig. 1. The ¼ inch plywood triangles, with pieces of carton adhered over the points to prevent puncturing of the blanket, permitted folding the blanket to form horizontal wedges as shown in Fig. 1.

The triangles measure 8 inches at the base and were 10 inches high, resulting in a treatment depth of 14 inches.

The ceiling was treated likewise (See Fig. 2.) and a rack with wedges was hung on the door. All area was so treated except for the floor, an opening of 2 by 3 feet to permit viewing through the testroom window, and an opening at the center of the ceiling for illumination.

It took two men two days to install this structure, and the cost of the materials was approximately $200.00.

Method

The arrangement of electrical equipment (for a list of equipment see page 525) is shown in Fig. 3. The motor of the recorder was mechanically coupled to the oscillator so that it would simultaneously drive the frequency dial of the oscillator and the recording paper, both at a predetermined speed. While thus scanning a selected frequency range, the voltage applied to the speaker did not vary appreciably, whereas the sound pressure at the microphone varied considerably.

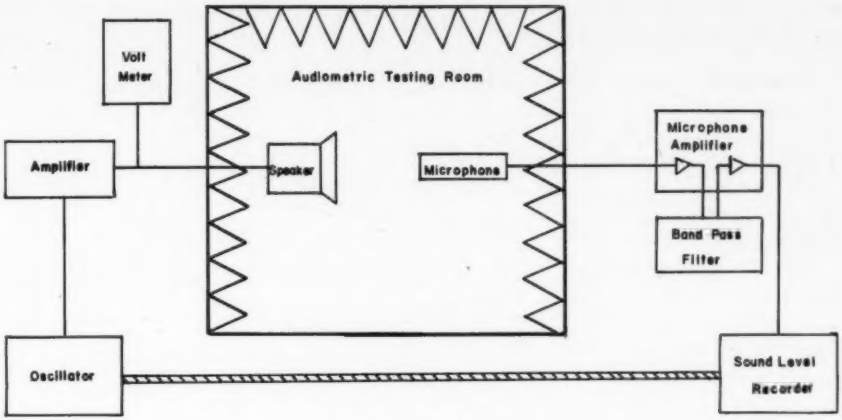

Figure 3

The experiment consisted of recording the sound pressure variation as a function of frequency, while keeping the microphone stationary 3 feet above the floor and pointing toward the sound source for

a) Bare walls.

b) Aerocor installed on walls and ceiling (as described under Installation of Acoustic Material, see Fig. 1 and 2).

Frequency scanning rather than the method of the traveling microphone (see Ref. 1) was used because the effect of the Aerocor acoustical treatment is much more clearly demonstrated in this manner.

Results

The tracings of Fig. 4 were obtained with an arrangement as shown in Fig. 3. The sound source, an eight inch speaker mounted in a ¾ inch plywood baffle 23 by 30 inches, was placed on the floor as shown in the situation sketch (see Fig. 4).

The oscillator and amplifier supplied a sinusoidal signal to the speaker with an amplitude of 1 volt and a frequency which was scanned from 200 to 5000 cps in a period of 230 seconds.

A wide band pass filter was inserted in the circuit which allowed frequencies from 75 to 9,600 cps to pass to the recorder. This was necessary to eliminate any low frequency components from distorting the results. The recording paper moved

at a rate of 3 mm/sec. Fig. 4 compares the recorded sound pressure level before and after installation of the aerocor on the walls.

The upper tracing was obtained before installation of acoustical material whereas the lower tracing portrays the sound pressure level variations with wedged aerocor blanket installed on the 4 walls and ceiling. In both cases the floor was covered with wall to wall carpeting.

In both tracings an irregular line composed of peaks and valleys is seen. These valleys and peaks represent changes in sound pressure levels with changes in frequency

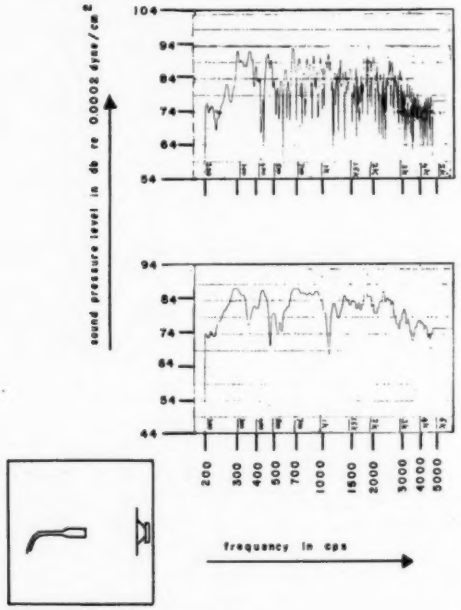

Figure 4

in a designated area of the test room as received by the stationary microphone. The lowest point of a valley is designated as a sound pressure "minimum". The number of minima and the depths of the valleys are greater in the untreated room when compared to the acoustically treated room. From this we infer that sound reflections from the surfaces of the acoustically treated room were less than those of the non-treated room.

Tracings were also obtained for frequencies from 5000 to 30,000 cps employing a high frequency speaker with the microphone directed toward and away from the speaker. The results were similar to those of Fig. 4, except for the effect of directivity which the microphone displays at high frequencies.

Conclusions

An audiometric testing room was converted into a semi-anechoic room. This was accomplished by installing on the existing walls and ceiling long wedges of a flexible blanket type fiberglas (Aerocor) 1 inch thick with a density of 2 pounds per cubic foot. Following such treatment, variations in sound pressure levels due to wall reflections were reduced considerably. To what extent the remaining variations are due to wall reflections and to what extent due to speaker characteristics or diffraction phenomena has not been determined.

The author is indebted to Dr. T. M. McGee for helpful discussions and to Mr. L. B. Lowery for his assistance during this investigation.

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List of Equipment

Oscillator:	B & K* Type 1013.
Amplifier:	McIntosh - Model MC 30.
Vacuum tube Voltmeter:	Balantine Model 300.
Speaker:	James B. Lansing Type D - 208 mounted on a ¾ inch plywood baffle 23 by 30 inches.
Microphone, Cartridge:	B & K Type 4131.
Cathode Follower:	B & K Type 2615.
Microphone Amplifier:	B & K Type 2603.
Filter:	Allison Model 2A.
Sound Level Recorder:	B & K Type 2304.
Audiometric Testing Room:	Industrial Acoustics Company Model 1200 SP.

*B & K Instruments, Inc.

THE EFFECT OF GROWTH HORMONE ON THE INCORPORATION OF N^{15} FROM AMMONIUM CITRATE, GLYCINE, L-ASPARTIC ACID, L-ALANINE AND L-GLUTAMIC ACID INTO AMINO ACIDS OF LIVER PROTEIN*

TRIESTE G. VITTI

Procedures developed in recently published studies[1] on the metabolism of N^{15} from four individual amino acids in untreated and growth hormone-treated hypophysectomized rats have been utilized to extend the scope of the former study, and to carry out a similar one dealing with incorporation of N^{15} from ammonium citrate into proteins of liver, heart, muscle, kidney, and spleen, and with distribution of the isotope among nine amino acids and amide nitrogen isolated from liver protein.

One group of seven untreated hypophysectomized rats, and a second group, similar in size and number, but treated daily for seven days with 100 μg. intraperitoneal injections of growth hormone, were both given N^{15}-labeled ammonium citrate containing 0.126 meq N^{15} per 100 g. of body weight, on the fifth experimental day. All animals were sacrificed 48 hours after injection of the isotope. Proteins from homogenates of liver, heart, kidney, and spleen were precipitated with TCA, washed free of lipoid material with alcohol-ether and also of nucleic acids with hot TCA[2]. Quadriceps muscles were processed to yield soluble sarcoplasmic and myofibrillar protein fractions, and an insoluble collagen-elastin fraction[3]. Amide nitrogen and nine amino acids were isolated from hydrolysates of gram-amounts of TCA-liver protein samples by ion exchange chromatography[4]. Relative amounts of N^{15} in nitrogen from protein and amino acid samples were calculated from 29:28 ratios obtained by mass spectrometry[5].

Similar N^{15} analyses were conducted on proteins, and their constituent amino acids, in liver tissue saved from the four series of animals used in the preceding study[1] in which the incorporation of N^{15} from glycine, alanine, aspartic acid, and glutamic acid into muscle proteins, and its transfer to their component amino acids, was investigated. Finally, distribution of N^{15} from alanine among amino acids of liver protein was determined in control and treated groups of rats sacrificed 24, 48, and 72 hours after administration of the N^{15} compound.

Growth hormone increased the incorporation of N^{15} from ammonium citrate into proteins of all tissues examined. Increases in weight and nitrogen content in growth hormone-treated hypophysectomized rats in the ammonium-N^{15} citrate experiment were much smaller for liver than for muscle, but N^{15} incorporation into liver protein was nearly twice as great as for muscle protein. Utilization of N^{15} from

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*From the Biochemistry Department of the Edsel B. Ford Institute for Medical Research and the Chemistry Department of Wayne State University. This is an abstract of a thesis presented to the Graduate School of Wayne State University in partial fulfillment of the requirements for the degree of Doctor of Philosophy. The degree was conferred in June 1961. The research work was done in the Biochemistry Department of the Institute under the supervision of Dr. O. H. Gaebler. This work was supported in part by research grant A-1362-Endo from the National Institutes of Health, U. S. Public Health Service.

ammonium citrate in protein fractions of skeletal muscle was smaller than that previously reported[1] for N^{15} from glycine, alanine, aspartic acid, and glutamic acid, but was close to that of glutamic acid-N^{15}.

Excepting the ammonium-N^{15} citrate experiment, the augmenting effect of growth hormone on incorporation of N^{15} was more striking in muscle than in liver proteins, due to the fact that while proteins in control livers were much more heavily labeled than corresponding control muscle protein fractions, concentrations of isotope in proteins of the two tissues were comparable in treated animals.

Although metabolism of nitrogen from aspartic acid and ammonia has been regarded as quite similar, present experiments demonstrate that the extent of incorporation and distribution of N^{15} in amino acids of liver protein are more nearly alike when ammonium citrate and glycine are compared as sources of the isotope, than when ammonium-N^{15} citrate is compared with aspartic-N^{15}.

Growth hormone caused an increased incorporation of N^{15} from all four of the N^{15}-labeled amino acids, into arginine of liver protein. This effect was even more evident when ammonium citrate was the source of N^{15}, and obviously offers no support to the idea that interference of growth hormone with urea formation might occur somewhere in the pathway leading to formation of arginine. These findings on arginine, together with the delay in disappearance of N^{15} from liver protein amino acids in treated animals, support the concept that the overall anabolic effect of growth hormone is due in part to its suppression of protein breakdown to amino acids.

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A NEW ORAL HYPOGLYCEMIC AGENT

PRELIMINARY REPORT

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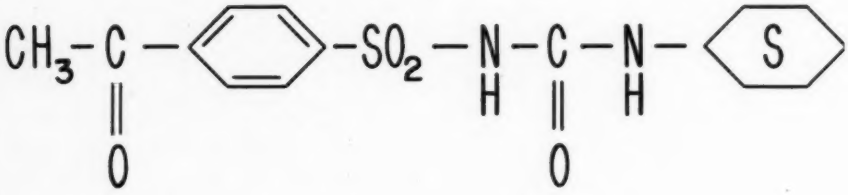
Division of Metabolic Diseases

This is a preliminary report on the use of a new oral hypoglycemic agent. 1(p-acetyl benzenesulfonyl)-3-cyclohexylurea (acetohexamide) is closely related chemically to tolbutamide (Orinase) and chlorpropamide (Diabinese). Acetohexamide is well-absorbed from the gastrointestinal tract. Sixty percent of an oral dose is reduced in the liver to its alphahydroxyl derivative, which is then excreted, along with acetohexamide, in the urine. Both compounds have hypoglycemic activity in the dog and the rat. Figure 1 shows the chemical structure of acetohexamide.



ACETOHEXAMIDE

Figure 1

Ten patients have taken acetohexamide, eight for more than three months. During this period, failure of hypoglycemic activity forced discontinuation of the drug in three patients; a fourth patient developed a mild maculopapular eruption seven days after initiation of therapy, and the amelioration of the diabetic state in a fifth has permitted therapy with diet alone. Table I summarizes the clinical data of the 10 patients. All patients have lipoplethoric (adult-type) diabetes. Six patients were receiving other oral agents at initiation of therapy with acetohexamide; one was taking insulin, and three others were treated with diet only. When acetohexamide was started, all patients needed more than quantitative diet to achieve good control of the diabetes. Five patients were successfully controlled with diet and acetohexamide. A skin reaction prevented further therapy in one patient, though metabolic control was good at the time of cessation of the drug. Two patients, following a secondary failure to tolbutamide, and one patient, following a primary failure with both tolbutamide and chlorpropamide, were refractory to acetohexamide.

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*Division of Metabolic Diseases.

Acetohexamide is well tolerated orally. Except for the skin reaction mentioned above, we have seen no systemic toxicity. Kirtley reports none.[1] In patients with insulin-deficient diabetes, acetohexamide, like the other sulfonylurea preparations, is ineffective. Acetohexamide may be tried when a secondary failure with either tolbutamide or chlorproamide has occurred and oral therapy is still desirable. Our experience is too limited to make any comments on the possibility of success in this situation. In daily doses of 0.5 to 1.5 gms., taken with breakfast, acetohexamide is an effective oral agent in treatment of the lipoplethoric diabetic who requires

Table I

CLINICAL DATA ON TEN DIABETICS TREATED WITH ACETOHEXAMIDE

Case	Age	Sex	Duration of Diabetes*	Prior Treatment	Amount**	Acetohexamide Duration	Result
1	70	F	5	tolbutamide 2° failure	1.5	6 mo	failure
2	56	F	12	chlorpropamide 250 mg/d	1.0	6 mo	good
3	67	F	1	diet	0.5	6 mo	good
4	54	M	15	tolbutamide 2° failure	1.5	9 mo	good
5	57	F	18	PZI-28 u.	1.0	7 d	skin rash
6	68	F	10	chlorpropamide tolbutamide (1° failure)	1.5	14 d	failure
7	79	F	6	chlorpropamide 100 mg.	0.25	3 mo	good
8	55	M	1	diet	0.5	3 mo	good
9	60	M	8	tolbutamide 2° failure	1.5	3 mo	failure
10	64	M	new	diet	1.0	6 mo	good

* in years.
** in grams per day.

more than diet for adequate control. The availability of acetohexamide probably will fail to broaden significantly the applicability of oral therapy in diabetes, but it will add greater depth.

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ACETOHEXAMIDE was generously supplied by the Eli Lilly Laboratories.

EXTENSIVE STASIS ULCERATIONS: REPORT OF A CASE

JOSEPH BENINSON, M.D.* AND HENRY G. BRYAN, M.D.*

Ulcerations of the lower extremities have many causes, most of which are secondary to venous stasis. Ulcerations of this etiology vary in extent from small denudations to widespread deep destruction of tissue. The following report of a case of far advanced lesions illustrates how much improvement may result from conservative therapy. Although complete healing had not occurred before the patient died from other causes, the degree and rapidity of improvement is noteworthy.

Case Report:

A 59-year old, white female with rheumatoid arthritis was admitted to the Dermatology In-Patient Department on July 8, 1960, because of large, tender, foul-smelling ulcerations on both legs.

The patient's history showed that during the previous six years there was gradual onset of swelling and tenderness of the knees, which prevented normal activity, and soon after she could not walk unassisted. At least three years before admission a "pimple", which healed only partially, developed on the lateral surface of the left leg. At approximately the same time she excoriated a small lesion on the right leg. Homemade dressings were applied to the ulcerations which persisted and enlarged.

During the eight months before admission the patient remained either in a chair or in bed and had to be carried about. She stated that it was at this time the ulcers developed a foul odor. Pain became increasingly severe, and on insistence of her family she sought medical care.

Physical Examination:

On admission she was a markedly obese woman in severe pain. (BP: 150/80; Pulse: 80/minute; Temperature 100 F) Four days after admission her weight was 229 pounds and height five feet six inches. Oral hygiene was extremely poor with numerous missing and carious teeth. The abdomen was protuberant, the skin relaxed at the umbilicus with a palpable defect in the wall approximately 12cm in diameter. Both knee joints were swollen and limited in motion. There were deformities and limitation of motion of the joints of the hands and wrists bilaterally. Enlarged inguinal nodes were palpable bilaterally. Both lower legs had large, deep, foul-smelling, tender ulcerations. On the right leg the ulceration occupied most of the middle third of the calf and contained two "pegs" of remaining subcutaneous tissue with overlying intact epithelium. The left leg had a large ulceration posteriorly as if a huge piece of tissue had been bitten out. In addition both legs had numerous satellite ulcerations measuring one to six cm in diameter. The bases of all lesions contained greenish purulent material. The ulcers were three to eight cm deep with tensely edematous overhanging edges (Fig. 1-6). Any manipulation of the ulcers elicited extreme pain.

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*Department of Dermatology.

Figure 1

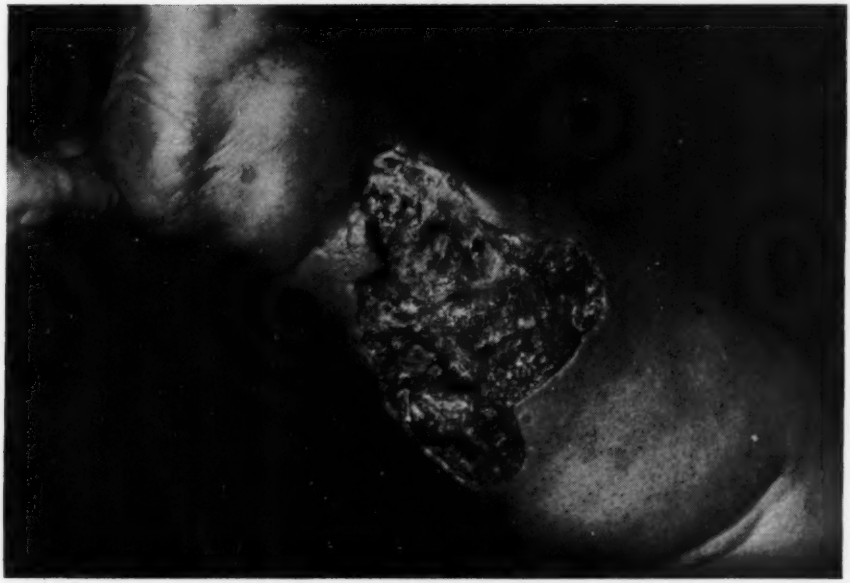

Figure 6

Figures 1 and 6. Photographs taken July 8, 1960. Extreme degree of ulceration and edema. Note small islands of remaining epithelium which are actually situated on top of "pegs" of tissue. These stalagmite-like "pegs" are actually 8 cm. above the base of the ulcer.

Figure 2

Figure 7

Figures 2 and 7. Photographs taken July 21, 1960. Appearance of lower extremities after two weeks therapy. Note that most of the edema has subsided, flattening the edges of the ulceration. The bases are free of nectoric material.

Initial laboratory studies showed hemoglobin 9.6 gm/100 ml; urea nitrogen 11 mg/100 ml; blood sugar 155 (later recorded as 205). VDRL was non-reactive. Serum protein electrophoretic patterns are illustrated (Fig. 11). Biopsy of the lesions showed non-specific ulceration.

The lesions were vigorously irrigated and cleansed frequently during the first three days of hospitalization. Pressure gradient dressings with Unna boots were then applied and the dressings changed as often as necessary, which early in the treatment was approximately every four days, but later was weekly. Adjunctive therapy consisted of diuretics, high protein diet (P-60 F-55 C-120) and complete bed rest with elevation of the lower extremities.

After four months of hospitalization, the patient's weight was 177 and hemoglobin 12gm. She was discharged and followed at weekly intervals in the Dermatology Out-Patient Department. The accompanying photographs show the change in character and gradual healing of the ulcerations (Fig. 1-10).

After seven months of treatment the patient developed symptoms of renal insufficiency, worsened rapidly, was readmitted to the hospital and died approximately two weeks later.

COMMENTS

Extensive stasis ulceration as illustrated by this case presents three major problems: First, such ulcers are painful. This patient complained of severe pain with either active or passive motion of her legs. Instrumentation, irrigation, or even gentle palpation of the eroded surfaces was extremely distressing to her. Any sudden movement of air against the lesions caused pain, and the patient had used make-shift dressings at home to alleviate this.

Second, is the problem of edema and self perpetuation of the lesions. Before hospitalization this patient spent much of her time sitting upright in a chair, a position which placed the legs under extreme gravitational pressure. Boggy, edematous, anoxic tissue will not heal normally, and progressive necrosis occurs. The excessive collection of extravascular fluid is conducive to further edema and ulceration.

The third problem is that of continual loss of fluid and serum (protein) from the denuded regions. This adds to the general debility of the patient.

Initial treatment of this patient consisted of application of pressure gradient therapy which has been previously described,[1,2] elevation of the legs, and oral diuretics to reduce edema. Gentle cleansing of the lesions removed superficial necrotic tissue and application of firm pressure gradient dressings promptly made the patient more comfortable. The involved regions were then covered and splinted, reducing pain. The dressings were applied firmly enough to prevent edema and to allow reepithelialization.

A study of the serum protein levels is of interest. At the time of admission but prior to active treatment, the electrophoretic pattern showed a reduction in

Figure 3

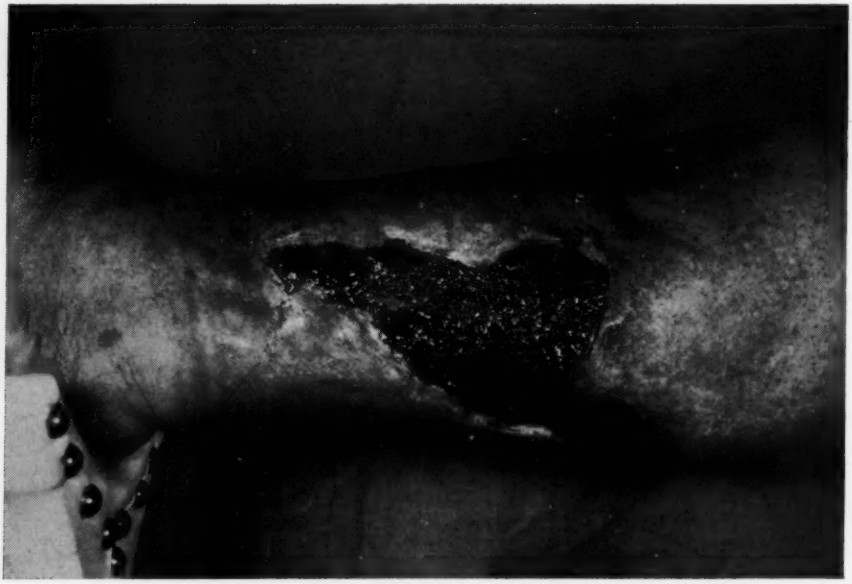

Figure 8

Figures 3 and 8. Photographs taken August 11, 1960. Bases of lesions are flush with surrounding skin. Epithelium is growing from the islands as well as borders of the ulcerations.

Figure 4

Figure 9

Figures 4 and 9. Photographs taken September 8, 1960. Marked reduction in size of ulcerations has occurred. Some smaller lesions have cleared completely.

Figure 5

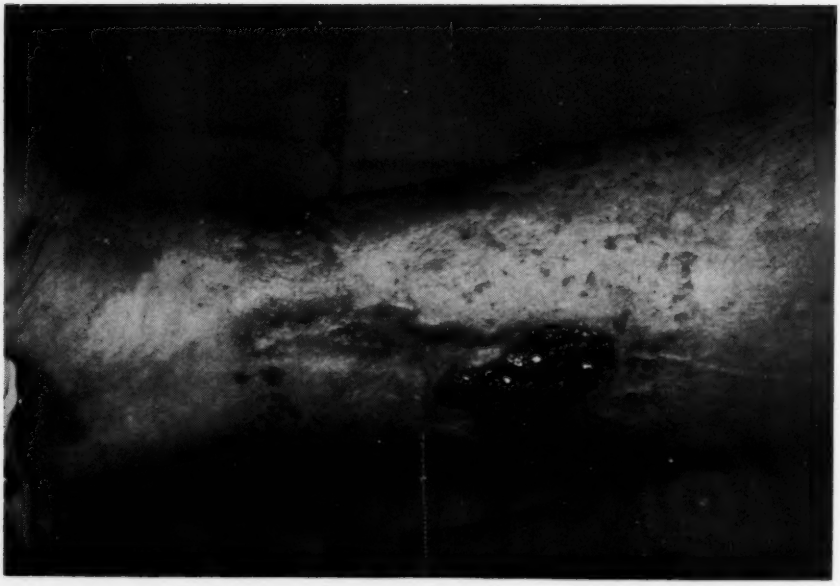

Figure 10

Figures 5 and 10. Photographs taken November 17, 1960. Further reduction in size of ulcerations. Original ulcerated surface is now partially covered with viable epithelium.

COMPOSITE CHART OF ELECTROPHORETIC PATTERNS

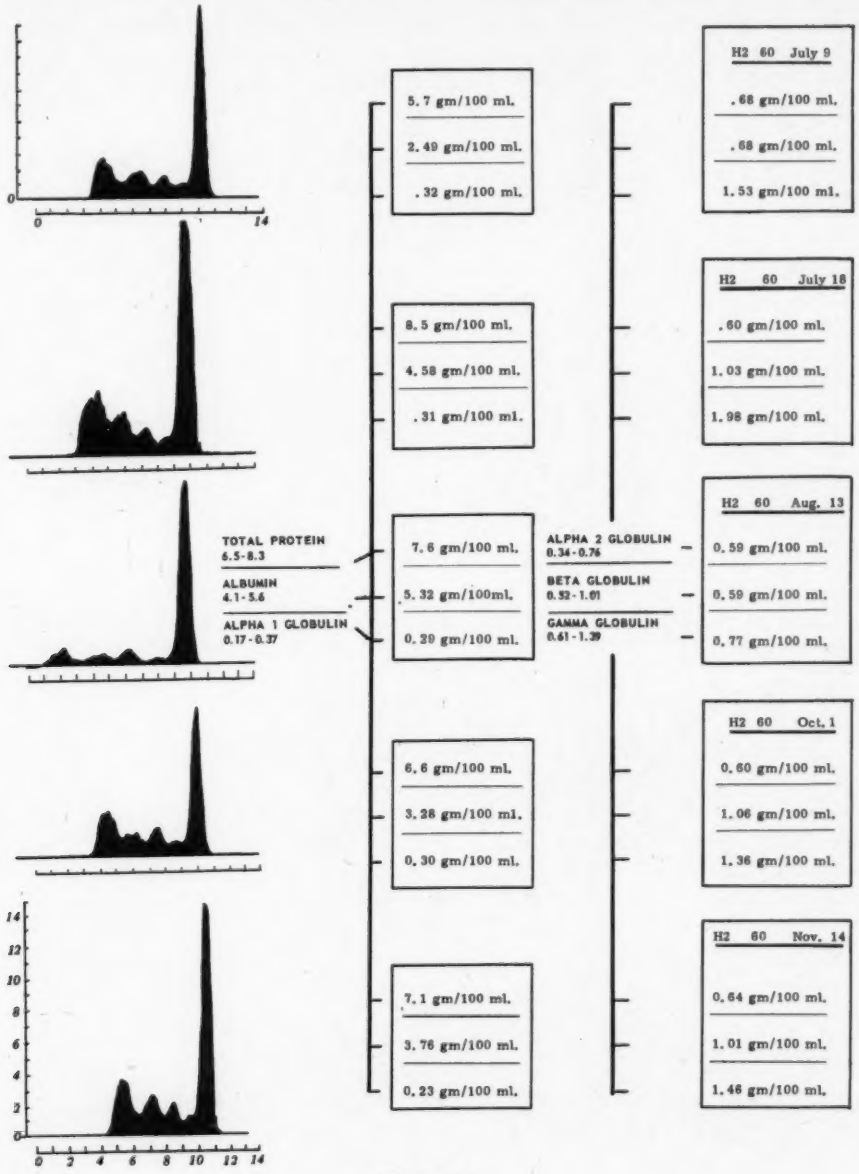

Figure 11

The serum albumen protein improved markedly with the applications of dressings; normal serum protein levels were maintained following this. Patterns were interpreted by Dr. Donald G. Remp, Department of Laboratories.

total protein and albumen. The second pattern, taken five days after application of dressings, revealed a significant elevation of the total protein and albumen fractions. This level is considered abnormally high; subsequent determinations are within normal limits. The third albumen determination is higher than expected and may include portions of the gamma globulin fraction in this determination.

We believe that this early rise to high and later reduction to normal levels may be comparable to the "Staub-Traugott" effect seen in diabetic individuals[3]. In diabetes there is a fall to lower than normal blood sugar level when the patient is given repeated small amounts of sugar. In other words there is evidence that an over-active physiologic process may occur in certain pathologic situations. In the case reported here the abnormal loss of serum protein was partially controlled by counter-pressure dressings while the body continued a greater than normal production of serum proteins. With partial correction of the protein losing process, i.e., occlusive dressings to the ulcerations, over-active production of serum protein continued for a short time before reverting to a normal level. A more familiar example of this effect is the formation of a bone callus larger than normal during fracture healing.

We are unaware of previous reports of such an effect expressed through serum protein levels.

SUMMARY

A case of extensive ulcerations of the lower extremities is presented to show what may be achieved with conservative therapy abetting the normal healing processes. An interesting side effect of serum protein levels was noted in this case.

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VOGT-KOYANAGI-HARADA SYNDROME

CHARLES P. HODGKINSON, II, M.D.*

Bilateral uveitis associated with one or more specific extraocular disorders has been reported for many years. In the twelfth century an Arab physician described white eyelashes associated with intraocular disease. Vogt[1] in 1906 was the first to report a case of non-traumatic bilateral uveitis associated with poliosis or white eyelashes, and recognized it as a disease entity. He also mentioned alopecia as an accompanyment of the disease, but did not include this in the clinical picture. Koyanagi[2] in 1929 reported six cases in detail and included in the syndrome vitiligo and dysacousia. Ten years later, Babel[3] stated that the disease should be called Vogt-Koyanagi syndrome and that it should include any non-traumatic bilateral uveitis associated with any or all of the symptoms of alopecia, poliosis, dysacousia, and vitiligo. In 1957, Bronstein[4] defined the concatanation of Vogt-Koyanagi disease as: a prodromal meningismal episode, followed by a non-traumatic bilateral uveitis, followed later by vitiligo, alopecia, dysacousia and poliosis. The inclusion of the central nervous system into the definition is a relatively new addition. It has been pointed out that many of the earlier case reports are somewhat vague and some of the symptoms now known to occur with the syndrome may have been overlooked or not emphasized in the published articles. Jonathan Hutchinson reported a case of "blanched eyelashes" in 1892, but the first complete cases in the English literature did not appear until 1931 when Parker[5] published two of his own and reviewed seventeen others. By 1939, when Babel suggested the name Vogt-Koyanagi, forty-six cases had been collected. Since then, the number of cases reported has grown considerably.

DISEASE COURSE

At the present time, the development of this disease is fairly well documented. Cowper[6] divides the illness into three stages: the meningeal, the opthalmic, and the convalescent stage. The meningeal stage is present in some form in at least fifty percent of the patients. The most frequent findings are a spinal fluid lymphocytic pleocytosis and elevated pressure. The patient may complain of any number of the following: severe headache, deep orbital pain, dizziness, lethargy, and general malaise. These prodromal symptoms have led to the suggested name of uveoencephalitis[6]. This first stage lasts two weeks to one month. The ophthalmic stage may be ushered in by a mild to a fumlinating uveitis. At this point, any number of the complications of uveitis may set in. When the fundus can be seen, it may show a diffuse choroiditis, retinal edema, and even optic papillitis. Occasionally, when the posterior uvea can be examined, a retinal detachment may be found. The detachments are typically bilateral and inferior. Deafness and tinnitus may occur at this time. Dysacousia seems to occur in about one-half of the cases.

Several weeks to as late as nine months after the onset of the uveitis, the remainder of the findings present themselves. Most commonly, they are present

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within three months after the start of the ophthalmic stage. Poliosis or white eyelashes is the most common and it occurs in from eighty to ninety percent of patients. Vitiligo, the next most common, is present in about sixty-three percent. Alopecia areata is the most frequently described type of hair loss, but total baldness is occasionally found. Alopecia has been reported in as few as fifty-three percent to as many as seventy-three percent of patients. The symmetry of the poliosis and vitiligo is often striking and they seem to occur most often on the head, neck, and trunk. All of the extraocular manifestations have a tendency to disappear spontaneously with time.

The convalescent stage starts when the skin and hair findings begin to return to normal. The uveitis usually recedes at about this time. As the media clears, one may detect a retinal detachment; this spontaneously decreases. The retina is said to have a peculiar orange color[7] and two types of "white spots" are described[8]. The first type is round and measures about one to three times the diameter of the central retinal vessels. They appear to be exudative in character and clear spontaneously as healing progresses. An irregularly-shaped spot may be seen early in the disease but soon disappears. The other type of spot observed in the third stage is permanent and seems to be of an atrophic nature. Cordes feels that they are due to cicatrix of atrophy of the choroid. The retina shows generalized depigmentation. This stage may last from six to twelve months.

The complications of this syndrome are those which may occur with uveitis. Glaucoma is the most frequent. This arises from occlusion of the pupil, secondary to complete posterior synechiae or from decompensation of the outflow mechanism. Secondary cataracts are also seen. Disturbances in vestibular function are seen occasionally as part of the general symptoms. Occurring with the skin disorders, may be edema of the scalp and seborrhea. Opticochiasmatic arachnoiditis has been reported.

The following case demonstrated some of the typical features of the syndrome.

R. D. was a thirteen year old Italian male who was first seen in the Henry Ford Hospital on June 24, 1960. His chief complaint was poor vision present for six or seven months. He stated that about four months ago, his eyelashes turned white and three weeks ago, his hair started to fall out. At the time of his first visit, he was an inmate of a state hospital for epileptics. The patient had been seen by another physician and was taking three milligrams of triamcinolone per day and using an unidentified eye ointment three times per day. He was also taking one grain of thyroid, phenobarbital, and Mysoline every day. The patient had not had a convulsion in one and one-half years.

Examination revealed a well-developed boy with white eyelashes, white eyebrows, and patchy loss of hair on the head. The vision was OD: 20/70 OS: 20/200. Slit lamp examination showed large, yellowish, mutton-fat keratic-precipitates on the endothelium of the left eye and many fine keratic precipitates on the endothelium of the right eye. Many posterior

synechiae were noted in both eyes. The anterior chambers were filled with numerous cells and a dense flare. The fundi were not visualized except for the bare outline of the discs and vessels. Intraocular pressure was OD: 8mm, Hg., Schiotz OS: 10mm, Hg. Schiotz with the 5.5 gram weight. The patient was admitted to the hospital and started on 40 mgm. of Prednisolone and Hydrocortisone drops topically. Complete blood count, urinalysis, lumbar puncture, audiogram, and electrolyte studies were all within normal limits.

By August 1, 1960, the vision had improved to 20/30 OU. At this time, the fundus was well visualized and numerous irregular, white atrophic areas in the peripheral regions were noted. These patches were about two to three central vein diameters in size. No areas of retinal detachments were noted.

On August 29, 1960, the hair on the head was noted to be turning white but was much thicker. The eyelashes and eyebrows were turning back to their normal black coloration. The vision had improved to 20/25 OU. The photographs show the external appearance when the patient was first noted, the retinal lesions when the fundi became visible, and the external appearance after treatment.

Figure 1

Figure 2

External appearance of R. D. on first clinic visit.

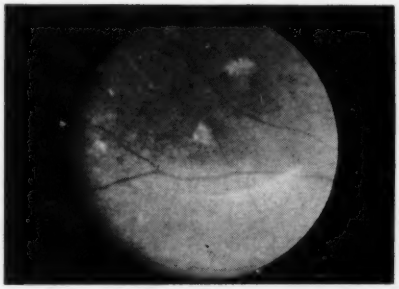

Figure 3

View of fundus when media had cleared.

Figure 4

External appearance after two-months of steroid therapy.

CASE DISCUSSION

This case represents a fairly typical incomplete Vogt-Koyanagi syndrome. The features missing when the patient was first observed were vitiligo, dysacousia, and the history of a prodromal meningismal episode. It is possible that the patient showed some, or perhaps all, of the features of the syndrome prior to his first clinic visit, but due to the previous enviormental situation, they may have gone unnoticed. The fundus lesions fall into one of the groups which Cordes[8] described. It is noteworthy to point out the improvement which occurred when steroids were administered. This cannot be considered a definite therapeutic response because the disease may have reached its peak in this patient and was about to enter the convalescent stage anyway.

ETIOLOGY

There have been many attempts to uncover a common etiological agent which could account for all the varied manifestations of this syndrome. The specific causative factor remains unknown. The one common element which seems to be present is the predisposition of the disease to occur in the more deeply pigmented races. The importance of this fact is not readily apparent. Rosen[7] feels that the work of Riehm gives greater importance to this occurrence. Riehm found that sensitization of one eye, by the injection of foreign protein into the other eye, could be accomplished only in pigmented rabbits. Schlaegel[9] was unsuccessful in confirming Riehm's conclusions. By directly inoculating albino and pigmented rabbits' eyes with normal horse serum and later injecting serum intravenously, he found equal gross and microscopic changes in the more severe reactors of both groups.

Tuberculosis and syphillis have been suggested as the cause of the disease, but the proponderance of evidence has been negative. Positive serologies and tuberculin skin tests are not constant findings. Vitamin deficiencies have also been suspected, but poor or no response to therapy guided along these lines has put this theory into the background.

Because of the extraocular manifestations, the endocrine system has been accused as the root of the trouble. It is well known that pigment disturbances of the skin and hair occur in adrenal and gonadal dysfunctions respectively. No evidence has been presented to bear out these suspicions.

There are two main etiological theories which have stood up. The first is the allergic theory. Peters[10] has been credited with first suggesting in 1912 that sensitization to uveal pigment could be the cause of this syndrome. Elschnig[10] two years earlier put forth this idea as the cause of sympathetic ophthalmia. Peters postulated that the deafness associated with the spontaneous uveitis was the result of the insult of the uveal antigen upon the pigment of the basilar membrane of the labyrinth. Koyanagi[10], however, took issue with this on the basis that the pigment of the basilar membrane is by no means a constant finding. It was also pointed out that the function of this pigment was not known. He felt that the time period when the disturbances occur, was inconsistent with a sensitivity reaction. On the other hand, other workers have continued to support Peter's theory[11]. Uveal

skin tests have proven positive in some instances[12]. Woods felt that the cases which give a negative reaction may have been present long enough for desensitization to occur. At the present time, many workers tend to be leaning away from the allergic theory, but there is no proponderance of evidence either for or against it.

The second etiological theory is viral causation. Hague[13] credits Bock in 1890 with the first association of ocular inflammation and the "virus of influenza". Davies[14] mentions that in 1910, Gilbert pointed out that herpes zoster was often associated with vitiligo. In the past twenty years, more and more workers have mentioned viruses as the cause of this disease.

In 1944, Hague[13] presented a well-organized theory to explain the varied manifestations of the syndrome. His explanation was based upon the interconnections between the hypothalamus, the pituitary gland, and the retina. He cites studies which showed fibers from the optic nerve entering the hypothalamus to extend to the supraoptic nucleus. He further described fibers running from the supraoptic nucleus and ending in the pars posterior and the pars intermedia of the pituitary. Thus retinal-hypothalamic-hypophyseal connections were demonstrated. Hague pointed out the influence of the pituitary gland in controlling pigment migration and also the power of light stimulation on the retina in affecting gonadal function. Hague felt that these fiber tracts mentioned mediated the alopecia areata, poliosis, and vitiligo. He stated that dysacousia may be tied in by involvement of fibers in the supraoptic decussation of Gudden which have been traced to the medial geniculate body. Hague stated that in his opinion, one and only one lesion could account for all the symptoms. This lesion is felt to be in the supraoptic-suprachiasmal region. He postulated that neurotropic viruses passed along the nerve pathways and settled in the hypothalamus causing local necrosis.

Attempts to isolate a virus from cases of the syndrome have been inconclusive. Woods[15] in a concise summary of the experimental efforts to isolate a virus from the affected cases, cited Takahashi's successful efforts in 1930. The cisterna magna of five normal rabbits was innoculated with bacteriologically sterile vitreous from a case of Harada's disease. Two of the animals developed optic neuritis and later a generalized uveitis. This worker also injected spinal fluid from the same case into the vitreous of rabbits and produced the similar ocular lesions. In the first instance, he found that he could transfer the disease to other rabbits. Walsh brings up the question of possible activation of dormant virus 3 disease which is, according to Rivers and Tiblett, widespread in the rabbit population. Malbran and Muhlmann injected bacteriologically sterile subretinal fluid from a case of Harada's disease into the subarachnoid space of rabbits and obtained an optic neuritis and uveitis.

Negative results were reported from the Wilmer Institute when mouse brains and egg embryos were innoculated with aqueous fluid, subretinal fliud, and spinal fluid from cases of Vogt-Koyanagi-Harada's disease. It was felt that the reason for the failures was because all the cases used were at a late stage. Bruno and McPherson[17] attempted mouse brain innoculations with subretinal fluid from some of their cases, but could not duplicate the results of the Japanese workers.

Some of the more recent work has been carried out by Ikui and Furuyoshi[18]. In 1955, they used aqueous, spinal fluid, and subretinal fluid as well as material from the uvea and vitreous in twenty-five blind successive mouse brain innoculations. No positive results were obtained from this or when they used the chorioallantoic membrane of chick embryos. They used similar material from seventeen patients and injected it into the vitreous of rabbits and obtained positive results when thirteen developed acute uveitis. When the ultra filtrate of the injected material was used, three cases of uveitis were produced in eight tries. In none of these cases was the fellow eye involved spontaneously. The microscopic examination of the affected eyes were reported to have many histologic similarities to the human cases. In 1953, Sugiera at al were actually able to isolate a virus after innoculating mice brains and carrying out four to eight blind passages. This virus was found to show a positive neutralization test with the serum of other patients in a dilution of 1:100.

In summary of the experimental work, it appears that while some results implicate a virus, the evidence is by no means conclusive. The well-known elusiveness to isolation of viruses is in itself consistant with the pattern of the investigational reports. At the present time, the virus etiology seems to be the most widely accepted.

TREATMENT

From the investigations to determine a causative agent has come little help in guiding therapy. A variety of therapeutic remedies have been employed. In general, those used for chronic uveitis have been tried. Sodium salicylate in large doses, potassium iodide, anti-luetic drugs, bromides, calcium, antituberculous drugs, large doses of vitamins, foreign protein, autoserum have yielded equivocal results. Recently, steroids have been employed and the results appear to be somewhat successful. Bronstein[4] in 1957 treated a case of Vogt-Koyanagi-Harada's disease with prednisone in large dosages and achieved apparent success. It is interesting that after one month when the dosage was lowered, the ocular symptoms flared. When the patient was again started on the medication, she was once more controlled. The uveitis remained quiescent when the drug was withdrawn. His conclusion was that steroid therapy should be maintained at a maximum therapeutic dosage for a prolonged length of time. Ikui and Furuyoski[19] stated that if the steroids are effective, they are only helpful for the ocular involvement and not for the associated findings. They also mention that rapid improvement may occur but relapses in three weeks are not uncommon. Mosci[20] has asserted that the response to steroids tends to implicate allergy as the cause of the condition. Other investigators[8,12,21,22,23] reported that the steroids did little or nothing to alter the course of the disease. Stadnik and McFadden felt that steroid therapy had even aggravated the disease in one of their cases.

Surgical treatment is confined mainly to the management of the complications of the anterior uveitis. Retinal detachment usually regresses spontaneously if given a sufficient time interval.

It is apparent that there is no one answer to the therapeutic management of this disease. The scattered reports of the successful use of steroids is encouraging. Any other treatment should be considered in the light of the individual case.

RELATIONSHIP BETWEEN VOGT-KOYANAGI SYNDROME, HARADA'S DISEASE, AND SYMPATHETIC OPHTHALMIA

As early as 1883, Nettelship[25] in reporting a case of sympathetic ophthalmia with white eyelashes, suggested a common pathologic process with that which was later to be called Vogt-Koyanagi syndrome. This suggestion has been amplified by investigators through the years. In 1926, Harada[26] in Japan described a disease which was characterized by bilateral involvement with massive subretinal fluid leading to detachment, but without anterior uveal involment. He stated that it occurred mainly in adults and usually ended in spontaneous re-attachment of the retina. Most of the cases showed pleocytosis of the spinal fluid. As more cases were reported, it became apparent that instances of Vogt-Koyanagi syndrome often showed spinal fluid pleocytosis and, further, that Harada's disease could frequently be associated with one or even all of the extraocular manifestations of the Vogt-Koyanagi syndrome, including the anterior uveal involvement. There has been much discussion in the literature as to whether or not the Vogt-Koyanagi syndrome and Harada's disease should be considered the same. Parker and Rados stated that alopecia and poliosis are integral parts of the Vogt-Koyanagi syndrome. Rados felt that these were not a constant finding in Harada's disease. He also stated that retinal detachment is rare and complicated cataract is never seen in Vogt-Koyanagi syndrome. It has also been stated that ocular inflammation was restricted to the anterior uvea in these cases. There have been objections to all of these assertations. First of all, retinal detachment has frequently been reported when the media allowed observation of the posterior pole. Furthermore, other observers have not been able to report consistency of alopecia and poliosis. Complicated cataract has also been reported.

The attempt to link sympathetic ophthalmia with the Vogt-Koyanagi syndrome has arisen mainly out of the reports of similar histological characteristics. Matsuoka in 1933 reported on the examination of the iris of a patient with spontaneous uveitis, poliosis, and leukoderma. The findings were identical with sympathetic ophthalmia. Yuge[27] stated that earlier Kitazawa and later Ogawa, Sugimoto, and Kodama disputed the histologic similarity between the two entities. It is generally felt that the material studied by these latter workers was probably from patients in the late stages of the disease. Recently, Yuge[27], Swartz,[12] and Hager[22] and others have reported very similar or identical histologic pictures in these two diseases. Schlaegel,[9] Ikui and Furuyoshi[10] in their animal innoculations mentioned previously, reported histologic similarities to those seen in man in sympathetic ophthalmia. In some eyes, which have required enucleation, the so-called Dalen-Fuchs nodules, which are frequently seen in sympathetic ophthalmia, have been reported.

An apparent inconsistency has been reported in the relationship between these two conditions.[28] Many cases of Vogt-Koyanagi syndrome have been seen in Negroes while sympathetic ophthalmia is definitely less common in this

race than it is in Caucasians. Woods[29] stated that the two diseases differ, from a histologic standpoint, only in the picture of the retinal detachment. In the Vogt-Koyanagi syndrome, the retinas show necrosis, depigmentation of the pigment epithelium, edema, and monocytic infiltration. He stated that these findings are only rarely seen in sympathetic ophthalmia.

All of the extraocular manifestations seen in the Vogt-Koyanagi syndrome as well as those in Harada's disease have been reported to occur in sympathetic ophthalmia. The only remaining component which gives hope of being a differential point is the connection of trauma with sympathetic ophthalmia. Even here, there are reports of cases of Vogt-Koyanagi syndrome being initiated apparently by surgical trauma.[12,30] Also reported are cases of sympathetic ophthalmia which occurred in relation to intraocular choroidal sarcoma and malignant melanoma.[28] The incidence has been estimated as one to three in every three thousand cases of ocular melanoma. Yuge[27] feels that inspite of the reports of trauma in connection with these diseases, the prophylactic effects of an enucleation should be considered. He states that in sympathetic ophthalmia, the disease will not occur if the eye is enucleated soon after the trauma, while progression will occur in the Vogt-Koyanagi syndrome. He proposes that sympathetic ophthalmia is an "eye-conditioned oculo-oto-cutaneous syndrome", while Vogt-Koyanagi's disease is non-conditioned. The general feeling seems to be that the Vogt-Koyanagi syndrome and Harada's disease are clinical variants of the same basic disorder resulting from different responses in individuals affected by a common etiological agent. In order to avoid confusion because of the two different names, Cowper has proposed the term "uveoencephalitis". The relationship of these disease variants to sympathetic ophthalmia is less clear. It has been stated that if the eiology is the same, the only difference in the diseases may be in the manner in which the initiating agent gains entrance to the eye. In the instance of viral etiology, the organism may reach the eye by direct innoculation in sympathetic ophthalmia and via the blood stream or central nervous system in uveoencephalitis, or be there already in either.

ADDENDUM

On July 12, 1961 the patient returned for a follow-up visit and two symmetrical patches of vitiligo were noted in the sacral region. The fine hairs in these areas were white. Another feature of this syndrome has thus appeared.

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ACQUIRED NON-FAMILIAL OSTEOMALACIA OF VITAMIN-D-RESISTANT TYPE

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Hypophosphatemia associated with vitamin D-resistant rickets has commanded increasing interest, yet despite the prominent clinical and metabolic features, the basic abnormality has not been defined. Winters and associates[1] have written extensively on the familial aspects, and they also reviewed evidence for and against defective renal tubular function, secondary hyperparathyroidism and vitamin D refractoriness as possible causal factors.

As might be expected for patients with familial disease, both skeletal abnormalities and hypophosphatemia have been recognized shortly after birth.[1,2] The designation "congenital" has been applied to the refractory rickets in such cases. In most, but not in all of these children, a familial basis has been established. In contrast, scattered case reports exist in which the earliest clinical expressions of osteomalicia appeared in adulthood, suggesting that latent familial and distinctly non-familial forms can occur. We are primarily concerned in this paper with the non-familial, non-congenital disorder, which hereafter is referred to as "acquired" refractory osteomalicia. Although similarities exist between this and the congenital type, certain differences can be recognized, particularly in the light of recent experiences with treatment. We will draw from information accumulated in the literature and from personal observations of two patients with presumably the acquired form, one of whom was previously reported in detail.[3] Additional observations have confirmed our early impressions that high dietary phosphorus, achieved through the use of phosphate supplements, is of therapeutic value to at least certain patients with acquired, vitamin D-resistant osteomalacia.

CASE REPORTS

Case 1. (H.F.H. #96 24 45)

H. F., a 60 year old salesman, first experienced low back pain in January 1959. Several weeks later, he noted ankle and foot pain which increased with weight bearing. General weakness and fatigue were prominent symptoms, and the back pain, aggravated by coughing and sneezing, gradually progressed in intensity to the point that motion, such as turning in bed, was almost unbearable. His general health otherwise was good, and historical evidence was lacking for dietary deficiency, diarrhea and renal calculi. When first examined in August 1959, he was considered to have a herniated lumbar disc, despite lack of neurological signs. In the initial laboratory studies, hemoglobin was 14 grams per 100 ml. and white cell count was 6500 with a normal cellular differential. Specific gravity of 1.019, acid pH and negative tests for protein and reducing substances were noted for the urine which on microscopic study was normal. Serological test for syphilis was negative.

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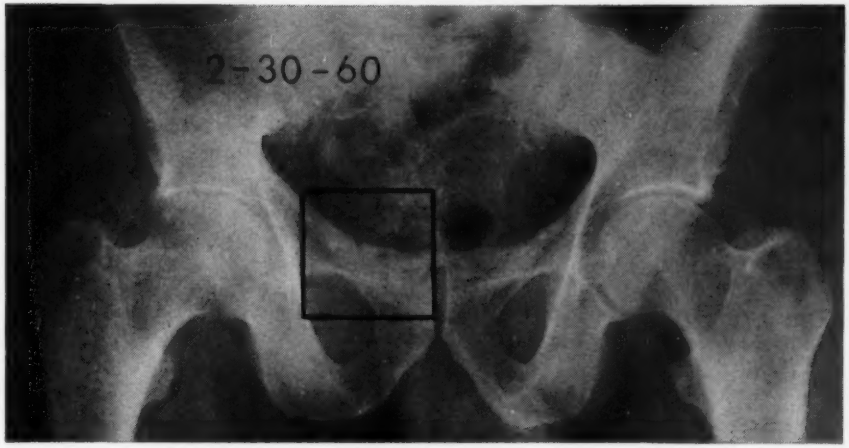

Figure 1a

Pelvic x-ray film demonstrating bony demineralization and pseudo-fracture, right superior ramus.

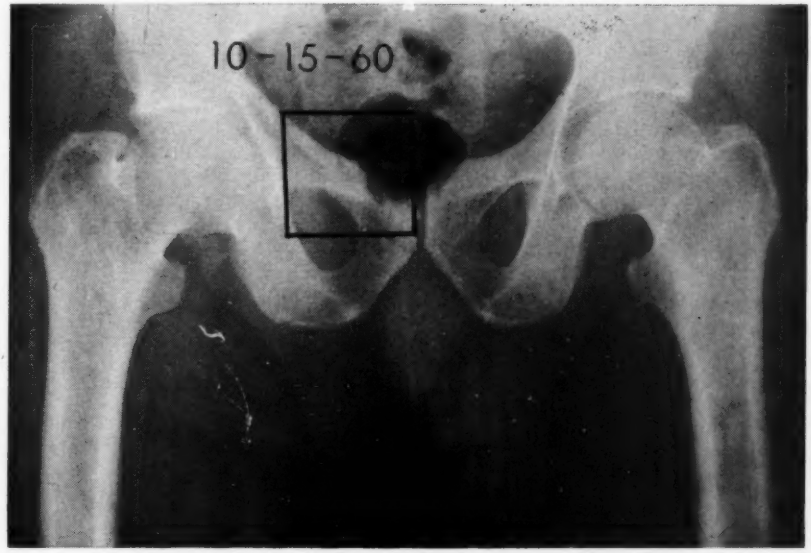

Figure 1b

Progress film after eight months oral phosphate feeding. Increase in mineral content of bone near site of pseudo-fracture is apparent.

When later the symptoms progressed in severity and the original diagnosis seemed untenable, additional studies were performed. Fasting serum sugar was 100 mg.,

Figure 2

Photomicrographs of undecalcified iliac crest bone prepared by the method of Frost.[4] Wide osteoid seams are demonstrated between the black bars.

carotene 125 mcg., creatinine 0.8 mg., calcium 10.3 mg., inorganic phosphorus* between 1.0 and 1.8 mg. and phospholipid phosphorus 10 mg. per 100 ml. Serum sodium was 137, potassium 3.8, chloride 96, and carbon dioxide 28.2 meq. per liter. Urinary calcium excretion was 87 mg. per 24 hours. Serum alkaline phosphatase

*Hereafter referred to as serum phosphorus

was 10 and 12 Bodansky units, while acid phosphatase was 1.2 K. A. units. Tubular reabsorption of phosphate (TRP) was 78 per cent (normal 86-95). Chromatographic pattern of urinary amino acids was normal.** Roentgenograms of the small intestine were normal. A linear zone of demineralization (pseudofracture) in the right superior pubic ramus was noted in the pelvic roentgenograms (Fig. 1-a). Widened and increased numbers of osteoid seams typical of osteomalacia were present in sections of bone (Fig. 2) obtained from an iliac crest open biopsy.

The family history was negative for evidence of skeletal disease. Blood relatives were not available to test for evidence of familial hypophosphatemia.

SPECIAL STUDIES

1. Renal Tubular Response to I. V. Parathyroid Extract and to I. V. Calcium.

   (a) Parathyroid extract, 200 units intravenously, produced less phosphaturic effect in the patient than in the control subject, while basal phosphate excretion in the patient was three times that in the control (Fig. 3).

   (b) Calcium gluconate, 15 mg. per kg. body weight, was given intravenously over a four hour period. Urinary phosphate excretion decreased approximately 50 per cent while TRP increased to normal. At this point intravenous parathyroid hormone was given (same dose and lot number as used above). Phosphate excretion rate increased as TRP returned to the original low value (Fig. 4).

2. Phosphate Absorption Tests.

   One hundred ml. of the special phosphate solution* was given in single oral doses to the patient and control subject, both being in the fasting state. For both patients an increase was observed in serum phosphorus concentrations, comparable in rate and degree (Fig. 5). A similar result was obtained following the simultaneous ingestion of calcium lactate (Fig. 6).

On the premise that the underlying defect was one of phosphorus depletion from hyperphosphaturia, treatment was begun with the special phosphate solution, 30 ml. orally six times daily. Within six weeks the patient reported complete relief of bone pain and tenderness as well as increased strength and sense of well-being. Treatment was continued, and eight months later laboratory studies were repeated. Serum calcium was 9.0 mg. and phosphorus, still depressed, averaged 1.8 mg. 100 ml. Urinary excretion of calcium was now only 7 to 20 mg. per 24 hours. Serum alkaline phosphatase levels continued increased at 9.9 Bodansky units, and tubular reabsorption of phosphate was even further reduced to 50 per cent. In pelvic x-ray films, a definite increase in mineral content was noted near the pseudofracture (Fig. 1-b).

The iliac crest was again biopsied and the previously mentioned histologic evidence of osteomalacia was still present.

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*196 gm. Na_2HPO_4 and 47.4 gm. NaH_2PO_4. H_2O in 4 liters aqueous solution
**Kindly performed by Dr. C. E. Dent of London, England

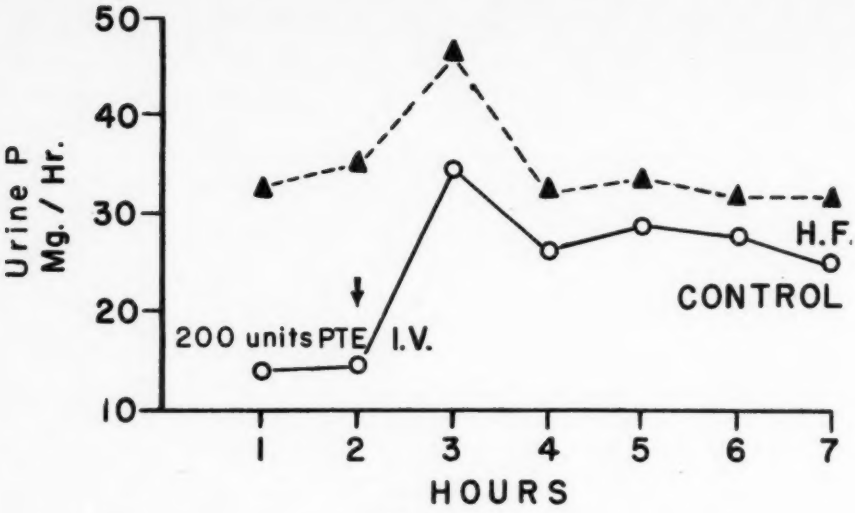

Figure 3

Effect of 200 units i.v. parathyroid extract (PTE) in patient H. F. and in control. The greater phosphaturic effect in the control (> 3-fold) as compared to the patient H. F. (< 1-fold) is evident.

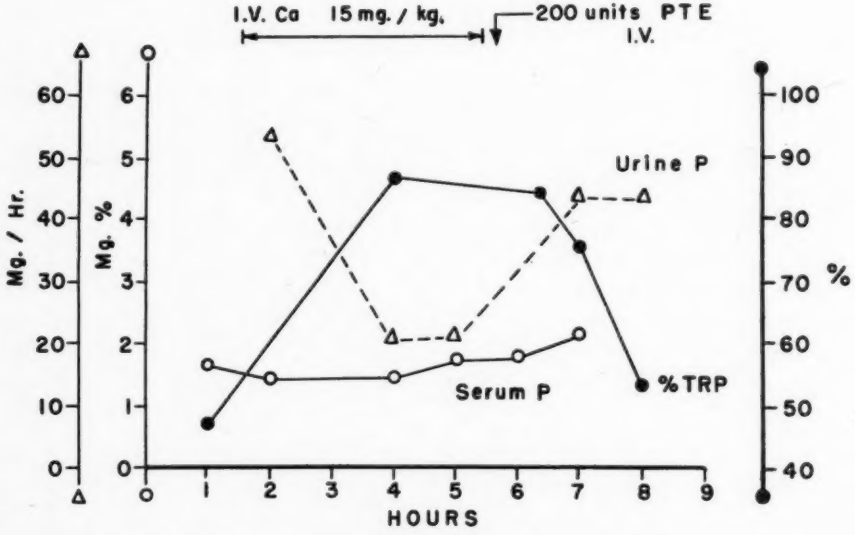

Figure 4

Effects of i.v. calcium followed by parathyroid extract (PTE) in patient H.F. During calcium infusion urinary phosphate excretion decreased concomitant with increased tubular reabsorption of phosphate (TRP). Parathyroid extract then increased urinary phosphate excretion and reduced its tubular reabsorption to the low base line level.

Case 2. (H.F.H. #60 83 72)

A. E., a 47 year old woman, was the subject of a previous report.[3] The clinical history, physical and biochemical findings, and skeletal roentgenographic and histologic observations were qualitatively similar but more severe than those of the first case. Initial treatment in 1950 with vitamin D, 100,000 to 180,000 units, and 3.6 gm. calcium lactate daily had not resulted in any measurable improvement. The addition of oral phosphate supplements, totaling 2 gm. of phosphorus daily, was followed by prompt relief of bone pain, healing of pseudofractures and improved metabolic balances for calcium and phosphorus. This combined treatment was continued for

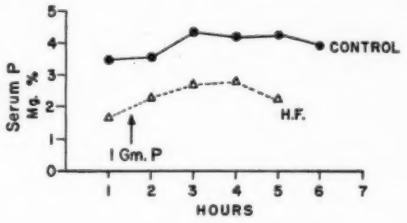

Figure 5

Response of serum inorganic phosphorus to oral phosphate load. (See previous footnote). Comparable rise is noted in patient H. F. and in control.

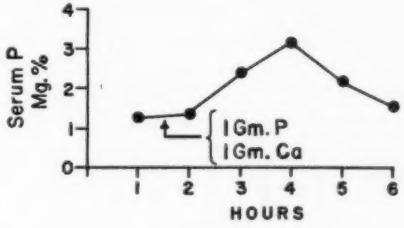

Figure 6

Response of serum inorganic phosphorus to simultaneous oral calcium lactate and phosphate solution in patient H. F. Note that ingested calcium did not interfere with absorption of inorganic phosphorus.

one year with sustained clinical improvement. Treatment with oral phosphate supplement alone was then given for one year with continued healing of pseudofractures and freedom from pain. In July 1960, ten years after the initial observations, serum calcium was 9.0 and phosphorus 1.5 mg. per 100/ml. Tubular reabsorption of phosphate remained low at 76 per cent, and serum alkaline phosphatase was still elevated at 12 Bodansky units. Pseudofractures have remained healed, but a coarsened trabecular pattern, particularly in the lumbar vertebrae, suggests a continuing skeletal abnormality.

CASE COMMENTS

Evidence was lacking in both patients for the more common causes of osteomalacia such as dietary deficiencies, malabsorption and hypercalciuria. The late onset of symptoms and absence of skeletal abnormalities in blood relatives suggested for both patients that the metabolic disorder was not familial. Serum concentrations of phosphorus were normal in the two sons and sister of patient A. E. Similar determinations were not possible in family members of patient H. F. Pertinent biochemical data were the normal levels of serum calcium, marked hypophosphatemia, increased levels of serum alkaline phosphatase and low urinary calcium excretion. Phosphate reabsorption by the kidney was impaired, while evidence was lacking for other tubular defects. Radiologic findings were those of osteomalacia, in keeping with the prominent and increased numbers of osteoid seams noted in bone sections.

In both patients the reduced TRP and increased basal phosphate excretion, when compared to the control subject, suggested the possibility of excessive renal

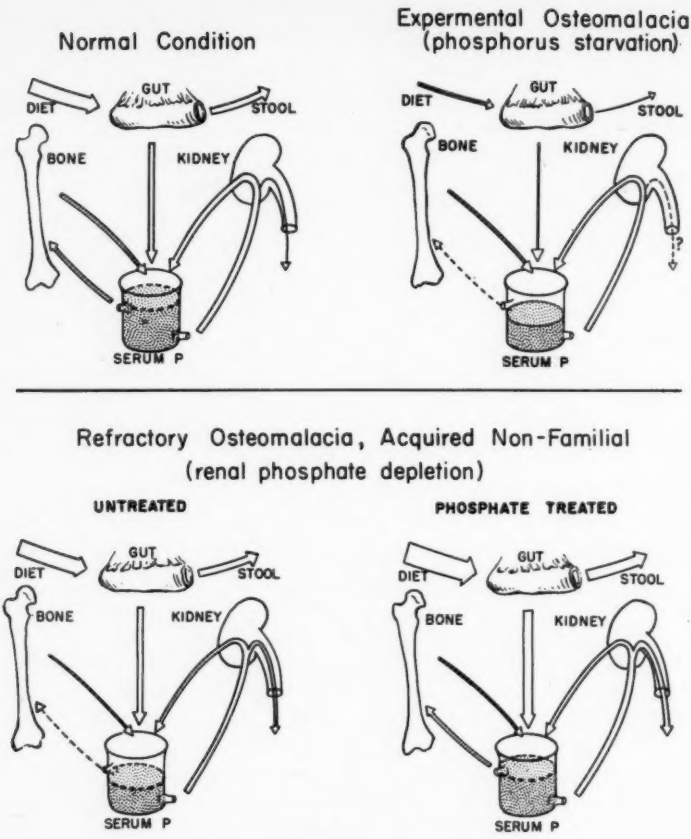

Figure 7

Schema of phosphorus movement. Width of arrows depicts magnitude of flow.

phosphate loss. Parathyroid extract exhibited only minimal effect on phosphate excretion, suggesting that either the tubules were already under maximal hormonal influence or, irrespective of the level of tubular activity, the kidney was truly refractory to the hormone. That the tubular defect was not "fixed" or unresponsive was suggested by the reduced phosphate excretion and improved TRP which followed intravenous calcium. This new rate of reabsorption was then reversed by intravenously administered parathyroid hormone. However, a purely glomerular action by infused calcium and the subsequent hormone could not be excluded.

The rapid rise in serum phosphorus observed in both patients following the ingestion of oral phosphate excluded the possibility that an absorptive block for this mineral was the primary defect. Calcium ingested simultaneously did not interfere with phosphate absorption, and no difference in the latter was noted between patient

A. E., receiving large amounts of vitamin D, and patient H. F. who was untreated. A significant reduction in urinary calcium occurred in both patients during phosphate therapy, and judged from the results of metabolic balance studies in patient A. E., calcium retention was materially enhanced. That this was clinically significant was clearly evident in the remineralization of the pseudofractures noted in serial roentgenograms for both patients.

The effects of phosphate feeding could be clearly assessed in patient H. F., who had not received previous vitamin D or other therapy. His favorable clinical course and improved skeletal status, judged by roentgenographic evidence, were similar to those of patient A. E. The latter, clinically and metabolically refractory to vitamin D, had made a striking improvement after phosphate supplements were added. As with patient H. F., however, presistent fasting hypophosphatemia and increased levels of serum alkaline phosphatase were indicative of a continuing biochemical defect. The question may be raised as to whether or not vitamin D contributed significantly or at all to her skeletal remission. Our opinion is that it did not and that augmenting dietary phosphorus was the decisive factor. The favorable effect of the latter in alleviating bone pain and improving skeletal mineralization in the two patients seems beyond question.

In respect to patient H. F., it cannot be said that he was truly vitamin D-resistant since this agent in conventional doses was not used in treatment. However, it is doubtful that the symptomatic response to vitamin D alone, even in large doses, would have been more effective than that which was observed with phosphorus. To further reverse the histological evidence of osteomalacia, prolonged treatment with prosphorus will undoubtedly be required. These high levels of total phosphorus intake, approximating three grams daily, have been well tolerated without evidence of impaired renal function. The latter is mentioned only because renal damage in rats has resulted from high phosphorus intake.[5]

The over-all evidence led to a final diagnosis in both patients of acquired non-familial osteomalacia of vitamin D-resistant type. The favorable response to treatment with oral phosphate was considered strong evidence that the basic disorder was phosphate depletion, presumably through hyperphosphaturia.

DISCUSSION

In their review, Winters and co-workers[1] found 65 reported cases of vitamin D-resistant rickets which they defined as a specific disorder, similar clinically, biochemically and radiologically to vitamin D deficiency rickets but resistant to this vitamin except in very large doses. In their judgment, the disease is almost always inherited and usually congenital. Considerably fewer reported patients appear to have had the acquired form of the disease. In the older literature, cases reported by Debray,[6] Milkman[7] and Leedham-Green[8] may have been examples of acquired vitamin D-resistant osteomalacia, but the evidence is inconclusive. Other more recently reported cases[9-19] are apparent examples of the acquired form. Bakwin's[20] case may also have been of this type despite the early age of onset. Swann[21] and others[10,13] have reported the interesting though unexplained association of neuro-

fibromatosis and acquired refractory osteomalacia. In their review of hereditary rickets and osteomalacia, Dent and Harris[22] record information on four young adults who apparently have an acquired but slightly different form, since increased glycinuria and mild acidosis were present.

Features common to the congenital and acquired types of refractory osteomalacia are the persistent hypophosphatemia, increased renal clearance of phosphate, decreased intestinal absorption of calcium and failure to respond to conventional doses of vitamin D. On the other hand, there are clinical differences to be recognized.

Muscular weakness, more characteristic of the acquired form, is often so profound as to limit activity and, in some instances, muscle wasting and adynamia are present.[14,18] The weakness is suggestive of that associated with hypokalemia, but this and areflexia have not been reported. We have noted that increased strength, an early sign of improvement following the institution of oral phosphate supplements, has occurred without concomitant increase in fasting levels of serum phosphorus. Meroney[23] observed muscle weakness in a patient with hypophosphatemia to improve after supplementary phosphate feeding. That depleted body phosphorus might result in imparied muscle function is not surprising in view of the importance of high energy phosphate bonds to muscular contraction. Whether or not intracellular phosphorus is reduced during extracellular phosphorus depletion is not known.

In contrast, the hypophosphatemia in congenital refractory rickets is not usually associated with significant muscle weakness. The authors have under observation three children with the latter condition, and all have normal strength and stamina. That age is not a factor in this difference is suggested by the occurrence of muscle weakness and adynamia in infants with vitamin D-deficiency rickets and hypophosphatemia.

In patients with the acquired type of refractory osteomalacia, bone pain and tenderness often restrict physical activity. When prolonged, this immobilization may result in superimposed osteoporosis such as we believe occurred in patient A. E. of the present report. In contrast, patients with congenital refractory rickets are usually free of skeletal pain and tenderness. This we have observed in three patients, despite persistent hypophosphatemia and radiologic evidence of marked skeletal deformities.

Differences in the clinical course of the two types might suggest basically different diseases. However, since the contrast is between a childhood and adult illness, the phenomena of growth and sexual maturation must be considered as possible conditioning factors. The congenital form tends to abate clinically and radiologically during adolescence. Serum concentrations of alkaline phosphatase often decrease to normal, although hypophosphatemia may persist.[24] On the other hand, the untreated acquired form of refractory osteomalacia is generally progressive, although Dent[22] has observed an apparent remission in the case originally reported by McCance.[9]

Winters and co-authors[1,25] have cited the considerable clinical evidence that vitamin D in large amounts facilitates healing of congenital refractory rickets. How-

ever, such therapy is not always effective and hypercalcemia may result. For these reasons, other therapeutic measures such as increasing dietary phosphorus have been tried. Evidence suggests that this approach, achieved by the use of oral phosphate supplements, is more effective in refractory osteomalacia of the acquired type. For patients with the later disease, results similar to those we are reporting have been observed by Henneman[16] and Jarowski[26]. Meroney[27] reported a positive calcium balance of 500 mg. per day in a patient with acquired refractory osteomalacia receiving a normal diet supplemented with four grams of phosphorus.

In contrast, neither radiologic evidence of bone healing nor improved mineral balances were noted in three children with congenital refractory rickets who received only phosphate supplements for a period of one year.[28] Likewise, Frazer in a personal communication to Winters[25] expressed a lack of confidence in such therapy for the congenital disorder. This apparent difference in response to phosphorus may be another distinguishing feature between the congenital and acquired forms. However, a plausible explanation for this refractoriness in children should not be overlooked. The normal phosphorus concentration in serum is substantially higher in children than in adults, and adequate mineralization in the former might occur only at the higher level. If true, even sizable amounts of dietary phosphorus may prove inadequate to "push" serum phosphorus concentrations in children to the higher level necessary for sketetal mineralization. Furthermore, the bone of children may have a greater competition with other somatic structures, such as muscle and liver, for available phosphorus.

In Figure 7 is schematically outlined the metabolic derangement for phosphorus in refractory osteomalacia of the acquired, non-familial type as it has been considered in the present report. For comparison, a similar schema is included for experimental osteomalacia in phosphorus-deprived rats,[29] which is also resistant to the action of vitamin D.[30] The central thesis for both is that phosphorus depletion alone, in the former from an apparent renal phosphate leak and in the latter from inadequate dietary supply, can result in osteomalacia. Suppressed calcium absorption is considered to be sequential to a hypophosphatemic block in skeletal mineralization. The parathyroids, if they have any role, would then serve to correct the hypocalcemic tendency which may occur early in the course of the disease. When phosphate is given in amounts adequate transiently to increase serum phosphorus levels in patients with acquired refractory osteomalacia, remineralization can temporarily proceed. The resulting utilization of serum calcium for mineralization then necessitates a secondary increase in calcium absorption. The above explanation is compatible with Harrison's[31] thesis that intestinal absorption of calcium proceeds at a rate which is dependent to a large degree upon the rate of skeletal mineralization. If correct, this explanation would relegate vitamin D to a role of questionable significance in both the pathogenesis and treatment of acquired refractory osteomalacia.

SUMMARY

The metabolic defect of refractory osteomalacia has been discussed in the light of recent knowledge concerning its natural history and treatment. Although biochemically similar, the congenital and acquired forms appear to have differences in the clinical course and response to treatment. The case histories have been

presented of two patients with the acquired form in whom favorable treatment with high dietary phosphorus stand in contrast to the poor results observed in patients with the congenital disease. Since phosphorus repletion alone may be beneficial, the thesis that vitamin D refractoriness is the primary defect may not be applicable to all patients with this interesting disorder.

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RENAL CYSTS — A CLINICAL ENIGMA*

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The proper diagnosis and management of renal cysts mimicking neoplasms can often be a source of great consternation to the urologist. In 1960 ten renal cysts were operated upon by the staff of our Department, that number being considerably more than in past years. Two cases of apparent renal cysts, one proven malignant and the other probably benign, and each managed differently will be presented. The subject shall then be reviewed and with the information divulged, we may then have a better insight into the proper management of such cases.

Figure 1

Left retrograde pyelogram showing tumor deformity of lower pole of left kidney.

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*Given before the Detroit Urological Association, May, 1961, Detroit, Mich.
**Division of Urology

CASE REPORTS

Case 1. (N.V.) This 59-year old WM was admitted on 12/6/57 for investigation of lower abdominal pain of one-week duration. The pain was associated with a feeling of distention and flatulence. He had no urinary complaints and gave no past history of genitourinary disease. P.E. was negative except for a ballotable and movable LUQ mass. The routine urine and blood studies were normal. A barium enema was taken which showed downward and medial displacement of the left colon. Because of this an IVP was done. The IVP suggested a tumor deformity of the lower pole of the left kidney. A left retrograde pyelogram confirmed this finding (Fig. 1). On 12/12/57 the left kidney was explored. Pre-operatively a cyst was favored. At surgery a large cyst was seen at the lower pole. However, by palpation it was firm and nodular and associated with large parasitic vessels and a nephrectomy was elected. The kidney was described grossly as showing a multiloculated cystic lesion. These cystic areas were said to contain clear yellow fluid. However, the linings were of variable thickness and irregular and showed numerous papillary areas (Fig. 2). The microscopic diagnosis was papillary adenocarcinoma of the clear cell type. The patient is alive and well today.

Figure 2

Normal renal tissue (at top) and papillary adenocarcinoma (at bottom) separated by layer of fibrous connective tissue.

Case 2. (C.A.) This 76-year old Negro male was admitted on 9/30/60 for treatment of a stasic ulcer. His past history indicated he had been treated for myocardial infarction three years previously. He had no genitourinary complaints

and gave no past history of genitourinary tract disease. P. E. was not remarkable except for the leg ulceration. No abdominal masses could be palpated. Routine blood and urine tests were normal. A chest x-ray showed considerable pulmonary fibrosis. Because of an ulcer-type history he had an upper GI series which showed a mass in the area of the left kidney. IVP's showed non-function of the left kidney and left renal mass (Fig. 3). An IV aortogram and nephrotomogram was then done and showed a patent left renal artery with some function of the kidney. Subsequently, left retrograde studies were attempted but only a bulb pyelogram could be obtained (Fig. 4). A tumor deformity of the upper pole was well demonstrated. Because of this advanced age, reluctance to submit to any surgery and suspected cardiac and pulmonary disease, needle aspiration of the mass was elected for a cyst was strongly suspected (Fig. 5). A clear serous type fluid was aspirated and contrast material was then injected visualizing a smooth contoured cystic mass. A cell block of the aspirated fluid was negative for malignant cells.

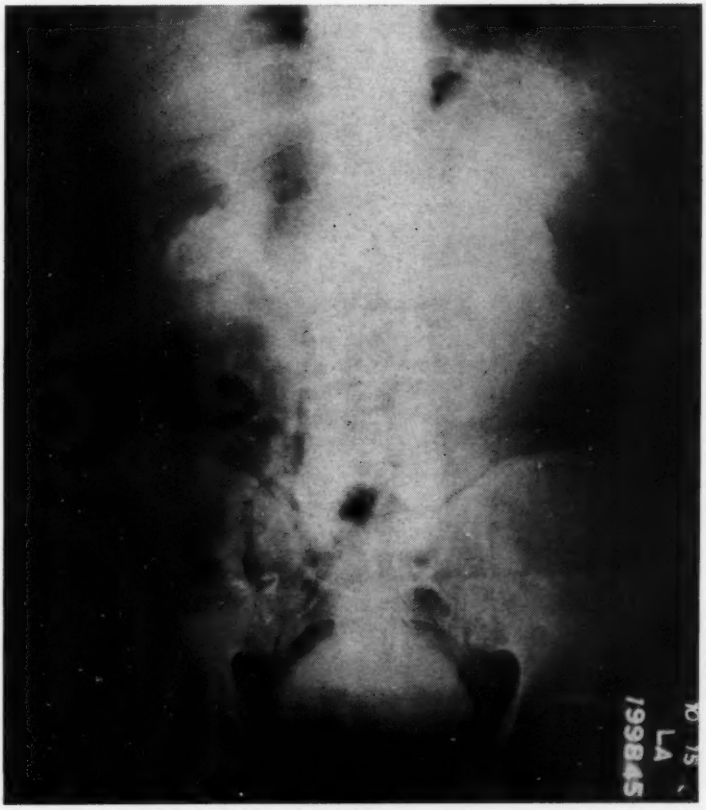

Figure 3

Intravenous pyelogram showing probably normal right kidney and non-function of left kidney with probable large left renal mass.

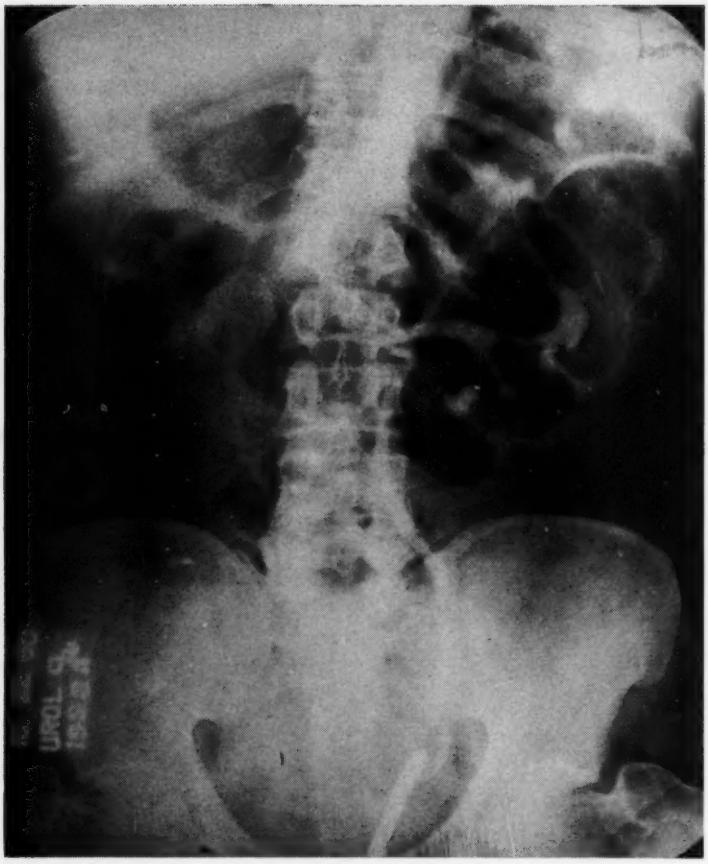

Figure 4

Left bulb pyelogram showing tumor deformity of the upper pole of the left kidney with downward displacement of the kidney.

PATHOLOGY OF RENAL CYSTS

The solitary or simple renal cyst that shall be discussed should first of all be distinguished from multicystic or polycystic kidney disease. Moreover, it should also be differentiated from cystic degeneration which is not uncommon in malignant tumors. By this time hundreds of cases of renal cysts have been reported. Moreover, it is said that solitary cysts are found in 3-5% of all autopsies. Oftentimes the renal cyst will be multilocular due to the presence of fibrous septa as was reported in one of our cases. The cyst fluid is usually either serous or hemorrahagic, although some detritus may also be present. Serous cysts tend to have a smooth cuboidal lining epithelium and the thin fibrous tissue wall may show tubular remnants. In contrast the wall of the hemorrhagic cyst is thicker and rougher and shows no

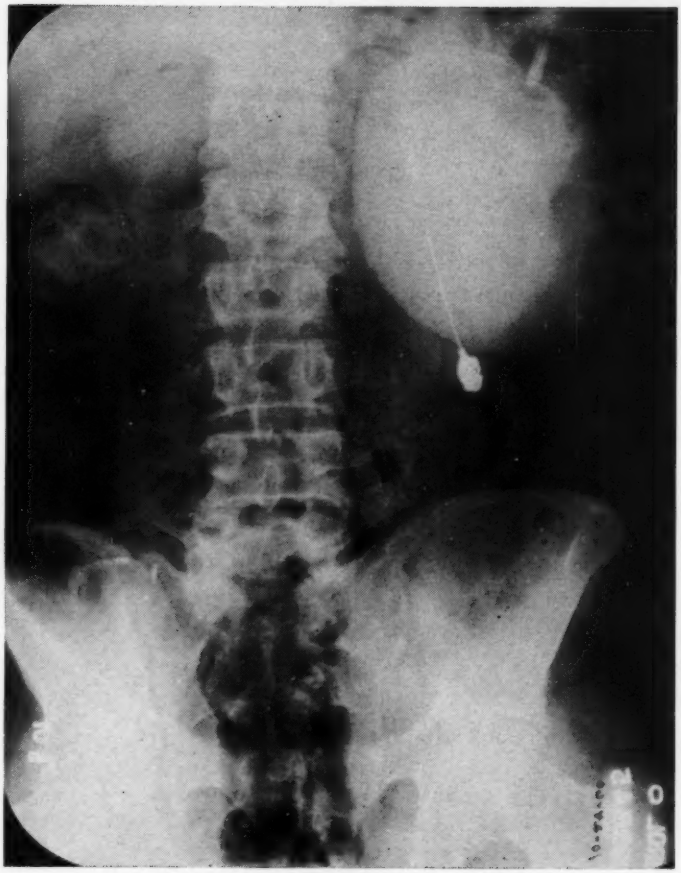

Figure 5

Cystic mass visualized by injecting contrast material through large spinal needle.

epithelial lining and is often covered with clotted blood. The cysts usually contain from 500 to 1000 cc of fluid and average 5 to 10 cm. in diameter, but much larger ones have been reported. The origin of these cysts is debatable, some regarding them as congenital and others as acquired. The incidence of these cysts is highest in people between 30 and 60 years old.

The matter of chief clinical concern is the question how often is malignancy found in these cysts? It is felt that malignancy is found in 7% of all cases of renal cystic disease. It should be pointed out, moreover, that the malignancy may not necessarily be within the cyst, but can be found in another part of the kidney, or adjacent to the cyst. Gibson,[1] in his review of renal cysts and tumors, expresses the opinion that the frequent association is due, not to tumor arising from the

cyst wall itself, but rather to the fact that a tumor arising in the parenchyma causes a cyst to form peripherally. This cyst later engulfs the tumor and creates the deceptive appearance. Hepler[2] was able to reproduce experimentally large renal cysts by a combination of tubular block and vascular occlusion. Gibson feels renal tumors reproduce this phenomenon clinically and postulates combined tubular and vascular block was the responsible mechanism in his report of three cases of renal cysts with malignancy.

While only 2% of serous cysts have been found to contain tumor, the incidence in hemorrhagic cysts is much higher, averaging about 25% in most series. When malignancy is found, it is always present in that portion of the cyst which is in contact with kidney tissue. The tumor may vary from a small nodule or surface irregularity to a large mass. Microscopically, the tumor is usually papillary adenocarcinoma of the clear cell type as was our first case. However, Wilm's tumor is not uncommonly reported in these malignant cysts.

SYMPTOMS OF RENAL CYSTS

Renal cysts if symptomatic, as indeed often they are not as was one of our cases and probably both, commonly cause pain in the region of the kidney. There may be recurrent attacks of pain that come with increasing frequency. If infection is present, fever and chills may accompany the pain. Not infrequently, the cyst may present itself as a palpable abdominal mass. Cholecystitis may be mimicked by upper pole cysts of the right kidney. Hematuria, gross or microscopic, may be another sign. Lower pole cysts usually act as retroperitoneal tumors producing organ displacement and compression.

DIAGNOSIS OF RENAL CYSTS

Radiography, although certainly not infallible, affords us the best clues as to the proper diagnosis of renal cysts. The flat plate will show a change in the outline of the kidney with a smooth, usually globular, shadow at the top, middle or bottom of the kidney. The pyelographic deformity depends of course upon the size and location of the cyst. The calyces may be altered in shape with compression or clubbing, and the pelvis may be enlarged. A change in the position of the normal axis of the kidney or partial rotation may also be produced. Some authors even feel that they can distinguish cysts from tumors with conviction radiographically. They cite the evenly contoured circular shadow and smooth crescentic calyceal compression associated with a clear line of demarcation between the mass and cortex as being characteristic of a cyst. Also these authors point out that cysts show a decreased density compared with the surrounding renal tissue and calcification may be present in the wall. However, it should be cautioned that these findings may be found in malignant tumors too.

MANAGEMENT OF THE RENAL CYST

It seems most prudent considering the available knowledge to advise surgical exploration in *all* such cases. The alternative offered to this approach, and especially advocated by Ainsworth and Vest[3] has been needle aspiration. The procedure

consists of needle aspiration of the mass and withdrawal of 30 to 50cc of fluid and subsequent injection of a similar amount of contrast medium. It is also suggested that the fluid be sent for cell block. Ainsworth and Vest cite the obtaining of clear fluid accompanied by a smooth contour of the renal cystogram as evidence of benignity. This procedure can usually be performed with great ease and little risk to the patient. However, several authors have tried to call our attention to the malignant potential of such cysts. Indeed, Lowsley[4], in reporting two such cases, asks for recognition of the term 'malignant cyst of the kidney'.

When surgical exploration is done, the ultimate procedure depends, of course, on the operative findings. If clear fluid is obtained from the cyst, and the internal surface is smooth, then the free cyst wall is removed and the margins sutured. Some surgeons apply phenol and alcohol to the part of the cyst wall adherent to the renal parenchyma. Nephrectomy is advised if the cyst has destroyed the kidney and the opposite kidney is normal. Moreover, it should be emphasized that nephrectomy is indicated in *all* cases of cysts which contain tumor or bloody or turbid fluid, or which present an irregular or roughened interior surface with detritus. It is also interesting to note that tumors associated with cysts appear to be slow growing so that the prognosis is somewhat more favorable than with the more common renal tumors.

SUMMARY

Renal cysts are not necessarily benign and this is especially true in those with hemorrhagic fluid. Surgical exploration is the treatment of choice. Whenever possible it obviates the missing of tumor either within the cyst or another part of the kidney. In poor risk patients, needle aspiration can be a useful and safe diagnostic procedure. Two case histories of renal cysts — one of which had proven tumor — have been reviewed.

It is only hoped that the preceeding material will instill a sense of gravity into a situation in which surgery, and the obtaining of histologic confirmation, can offer the only real assurance and potential cure.

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KWASHIORKOR ON THE NAVAJO INDIAN RESERVATION:

A discussion of the disease as seen throughout the world and a report of three cases in Navajo children

CHARLES B. WOLF, M.D.*

Kwashiorkor has been called the most prevalent and serious nutritional disturbance and the most important medical problem among children in the world today[1]. It is prevalent among all underprivileged peoples in the tropical and sub-tropical countries throughout Africa, Asia, the Far East and Central and South America[1]. The first cases reported from the United States[2] involved four Negro children in Louisiana who were older than the usual age for this syndrome (one was twenty years old) and were so heavily infested with roundworms that one of the authors of the report[3] admitted the worms may have caused the protein deficiency state. Jelliffe[4], in his excellent review, alluded to an occassional case having been seen in New Orleans but he may have been referring to the above mentioned four cases.

The cases to be reported in this paper are more similar to the cases of kwashiorkor seen in other areas of the world and are perhaps the first cases of "typical" kwashiorkor to have been reported from the United States.

The syndrome as described in African children consists of:

1. retardation of growth in the late breast feeding, weaning and post-weaning ages
2. alterations in hair and skin pigmentation
3. hypoproteinemia and edema
4. a variety of dermatoses
5. fatty infiltration, necrosis and fibrosis of the liver
6. gastrointestinal disorders including anorexia, vomiting, diarrhea and steatorrhea
7. irritability and apathy
8. a high mortality rate.

In a series of one thousand cases the usual age was four months to five years with eighty-five per cent of the cases in the seven to thirty-six months age range[1]. Jelliffe[4] divides the cases into those with "pure" kwashiorkor (protein deficiency but a sufficient intake of calories to maintain body fat) and nutritional marasmus (deficiency of calories as well as protein). His criteria for the diagnosis of kwashiorkor are:

The opinions expressed in this article are those of the author and are not to be construed as representing policy of the U. S. P. H. S.

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1. pitting edema
2. low body weight
3. wasted muscles with overlying fat of normal thickness
4. apathy or a "silent, listless inertness".

Often found, but unnecessary for diagnosis, are hair changes (hypochromotrichia, sparseness and easy pluckability), the classical "flaky paint" dermatosis, loose stools and signs of associated vitamin deficiencies, especially ariboflavinosis. The patient with nutritional marasmus has a very low weight, marked wasting of both muscle and subcutaneous fat and no edema or significant apathy. Edema is present in only one form of advanced malnutrition and that is kwashiorkor. Marasmus and nutritional dwarfing are not associated with edema. In marasmus the decreased protoplasmic mass presumably contains a normal *proportion* of protein[5].

Children with kwashiorkor are underweight in spite of the edema. The edema involves the feet, hands and genitalia but ascites is rare. The urine contains but a trace of albumin. There is hypoalbuminemia. These features, plus the response to the feeding of protein, lead to the conclusion it is indeed a protein deficiency state[1].

There is a dyspigmentation of the hair and skin. The hair lacks lustre and becomes pale or almost red[1]. The skin lesions are not characteristic. It has been argued the dermatosis is that of pellagra but the rash involves irritated areas, such as the diaper area, and not exposed areas as in pellagra[1,2]. There are definite geographic differences (perhaps dependent upon the type of vegetable protein in the diet). For example, in India there are color changes at the periphery of the hair which create a halo effect[2].

The non-purulent dermatitis usually consists of a dried skin that peels easily, without bleeding, and exposes a pink or white skin underneath (in a dark complexioned person)[1]. Lassitude, apathy, photophobia and the picture of dejection and misery characterize the youngsters. There are frequent bouts of diarrhea and usually some degree of anemia which is almost always normocytic or slightly macrocytic[1].

The literature pertaining to this condition is now large in keeping with its rank as a leading cause of world-wide morbidity. There have been biological investigations of extremely high calibre. Some workers believe the liver elaborates increased amounts of ferritin which acts as an antidiuretic[4]. There is a decrease in pancreatic enzyme activity as in starvation from any cause and this is perhaps the reason for the distressing diarrhea[4]. The anorexia and pancreatic insufficiency lead to further and more complicated malnutrition (superimposed marasmus).

Gomez et al[7] reported the "recovery syndrome" (seen in the Western Hemisphere) in which after successful treatment the liver enlarges with obvious signs of a collateral circulation and there is an increased eosinophile count and a hypertrichosis. In the Spanish-speaking countries of this hemisphere kwashiorkor (which means "red boy" in the Ga language of the Gold Coast) has been called

"syndrome pleuricarencial de la infancia"[4]. As in Africa and Asia it occurs when mothers' milk becomes inadequate for the needs of growing children and there is no complement of protein of high biologic value[4].

Not all the serum proteins are depressed to the same degree. Albumin and beta globulin are relatively more depressed than the other globulin fractions which are only slightly altered. Jelliffe and Edozien[4,9] cite Gitlin's study of radioactive preparations showing the hypoalbuminemia to be due to decreased synthesis. The serum albumin rises to normal with recovery so it would seem the depression is not due to liver damage because the liver is the principal site of synthesis and there is a prompt response to the furnishing of a proper protein in the diet.

The preferred treatment is not parenteral protein as was originally thought but is the furnishing of suitable protein by mouth. Skimmed milk preparations are most widely used and a gastric lavage is often necessary when anorexia is present[8]. Success is usual except in terminal states by using proteins of high biologic value-cautiously introduced, then vigorously administered. Recovery occurs in seven to ten days in most series. There is first a loss of weight due to loss of edema fluid then a true gain in body weight occurs[5].

The following cases were diagnosed and treated at the P.H.S. Indian Hospital, Tuba City, Arizona, between October, 1960, and March, 1961. The environment differs considerably from that of previously reported cases of kwashiorkor in that the altitude is over 5000 feet, the climate is most dry and the temperature ranges from moderate in the summer to below freezing in the winter.

R. A. (008836), a 1½ year old Navajo girl, was brought to the hospital because of swelling, irritability and anorexia of one week's duration. History was inadequate. She had been seen at the clinic previously for pharyngitis and the parents considered her to be well until the onset of edema. She had received "no milk for a long time" and had rarely been given meat. Her diet consisted primarily of tea, soda water and beans.

The child was intensely irritable. She did not appear malnourished. The hair was normal and there was slight edema of the eyelids. Ascites was thought not to be present. There was no dermatosis but there was a pitting edema of the hands and feet. The remainder of the physical examination was normal; the weight was 21 lb., 1 oz.

Initial laboratory study revealed a trace of albuminuria; hg. 9.5 gm., wbc 14,000 with a normal differential count. Total serum protein was 4.8 gm. per 100 ml., the albumin was 2.32 gm. per cent. The urea nitrogen was 8 mg. per 100 ml. and the cholesterol was 164 mg. per 100 ml.

The patient was given 0.6 ml. of a standard polyvitamin mixture per day and was fed whole milk and pureed meat thrice daily. After three days she was described as a "fair eater" and at seven days the weight had fallen to 18 lb., 1 oz. and the edema disappeared. From that point her behavior improved, she became

quite placid and was described as a "good eater". Ten days after admission her hair began falling out and continued to do so for the next four days when the process ceased just short of total alopecia. The few remaining hairs were definitely dyspigmented and could be easily and painlessly plucked. The happy, edema-free youngster was discharged on the nineteenth day — the weight being 19 lb., 4 oz.

Urinalyses revealed an occassional trace of albumin. Nine days after admission the serum protein was 4.65 gm. per cent, albumin 2.15 gm. per 100 ml. Fourteen days after admission the thymol turbidity was 9 units (normal under 4) and the g.o. transaminase 42 units. The parents demanded release before the follow-up protein determinations could be performed. The Mantoux test was negative as was the chest film.

N. S. (009252), an 11 month old Navajo girl, was brought to the clinic because of swelling and was admitted. She was said to have been well until 4 months before when swelling of the hands, feet and labia was noted. Since that time she had refused to eat well and had lost weight. There had been intermittent vomiting. The edema recurred 1 day prior to admission and according to the mother it made the child appear less starved. She had had skin trouble "for a long time". It was impossible to obtain a feeding history and quite possibly the child was cared for by siblings as is so often the case in a Navajo group.

The patient resisted examination in a normal fashion and was not apathetic or irritable. The hair was normal. The liver was not palpable and the heart was considered normal. The labia majora were markedly edematous. She had edema of the hands and pitting edema of the feet and lower legs. There was a patch of erythema on the nape of the neck with flaky skin overlying it. A dermatitis behind the ears was more characteristic of pyoderma. There was angular stomatitis and cheilosis. The weight was 15 lb., 13 oz.

Initial laboratory findings were a hg. of 10 gm., wbc 13,800 with a normal differential. The urinalysis was negative; the total serum protein was 4.5 gm. per cent.

Meat was ordered three times daily and no supplementary vitamins were given for 5 days. The cheilosis and neck lesions remained unchanged; the impetigo was erased by an antibiotic ointment. The cheilosis disappeared after vitamins were ordered.

One week after admission the weight curve had reached its nadir — 13 lb., 11 oz. The skin hung in loose folds and she appeared quite marasmic. At that time she began to eat well, and she became more lively and began to gain weight without the reaccumulation of edema. One week after admission the total serum protein was 5.15 gm. per cent; the albumin fraction was 2.35 gm. Two weeks later the serum protein was 6.88 gm.; the albumin 3.48 gm. The chest film and tuberculin skin tests were normal.

One month after admission the weight was 17 lb. and the patient seemed to be fully recovered. The dermatitis on the neck had persisted, the bacterial and fungal cultures from the skin being negative. A tension pneumothorax with

Staphylococcal empyema developed and was treated with closed thoracotomy and appropriate antibiotics. She later was sent to another institution for open thoracotomy and upon return was quite well, the skin was clear and the protein determinations at the other hospital were normal.

M. B. (007646), a two year old Navajo girl, was admitted because of sudden swelling. One month before a mild diarrhea began which ceased 2 days prior to admission at which point the edema occurred. The child had been increasingly more listless. For the month during which there was diarrhea the child was fed nothing except "soup" and soda water and occasionally whole milk. The pregnancy and delivery were normal and she had not previously been ill. She had received vitamins until 2 months before and they were restarted a week before admission — a supply having been furnished by missionaries.

The girl was listless, irritable and manifested generalized edema with palpebral and ankle edema being most prominent. There was no pleural fluid or ascites and the liver was not palpable. The most striking finding was an erythematous rash on the gluteal and perineal skin and on the extensor surfaces of the elbows. The rash extended up the back and down the thighs. It did not resemble "diaper rash" as it is commonly seen and the skin was flaky and peeled easily without bleeding. There was cheilosis and glossitis. She was afebrile; the weight was 23 lb.

The initial laboratory study revealed a normal urine, wbc of 28,000, 75% lymphocytes. The total serum protein was 5.0 gm. and the albumin 2.2 gm. per 100 ml. The blood urea nitrogen was 8 mg. per 100 ml., the thymol turbidity 7.7 units and the hg. 13 gm. per 100 ml. Studies of the skin for fungi were negative. Tuberculosis was ruled out.

The patient was given the regular pureed ward diet with whole milk and no vitamin supplement. 50 ml. of lyophilized plasma were administered on each of the first two hospital days. Edema disappeared on the 4th day — the weight then being 22 lb., 11 oz. On the 10th day the weight had fallen to 20 lb., 3 oz. She gained weight steadily after that. Four days after admission there had been no change in the severe dermatitis and vitamins were then ordered. The skin was normal 6 days later. The liver never became palpable. Improvement in behavior and appetite was noted 5 days after admission and by 7 days she was a model patient. Thymol turbidity 3 weeks after admission was 9.0 units.

It is not surprising that kwashiorkor exists among the Navajo people. There is profound poverty combined with the lack of knowledge of what constitutes an optimum diet plus the fact that infant care is often delegated to siblings while the mother tends her sheep. In addition to breast milk the children usually receive the gravies from stews or the water in which beans were cooked. Later the child may be given a piece of fat or fried bread to chew. It is unusual to find a person whose sole momentary occupation is feeding a child — the child may be given spoonfuls of a juice while the mother is eating and in some areas of the reservation a piece of pre-chewed meat may occassionally be given the baby. The diet rarely

approaches an adequate caloric bulk or adequate composition until the child's motor development is such that he can maneuver around the dining area and successfully delve into the pots of food[10]. Blatant malnutrition is common. Proper study of disease in the Navajo people is difficult because of the formidable language barrier, the extreme cultural differences and the inability of the historians to express time in terms of weeks and months. Because of the sparse laboratory figures this report serves only to indicate that the cases here reported are cases of kwashiorkor. Each patient did not exhibit the multiplicity of pathological changes as is usual in Africa but each exhibited more than are necessary to make the diagnosis of kwashiorkor as established by Jelliffe[4]. Where it was possible to perform sufficiently frequent laboratory studies it appeared that the edema disappeared and that there was improvement in the clinical status before the serum albumin had risen to a normal level.

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REFERRALS FROM THE SOCIAL SERVICE DEPARTMENT TO THE MICHIGAN DISTRICT OFFICES OF VOCATIONAL REHABILITATION*

A study to assess the adequacy of the referral methods employed by the Social Service Department

NANCY LOUISE LEWIS**

The purpose of this study was to assess the adequacy of the referral process of the Social Service Department to two Michigan District Offices of Vocational Rehabilitation (DVR), in an attempt to determine whether or not there were any procedures of the Social Service Department that could be improved. Such a study seemed indicated in that both agencies have as their major function the rehabilitation of the disabled individual, and in view of the concern today over the need for better coordination of services for the disabled. The findings, therefore, are interpreted in light of the effectiveness of the service to the disabled individual, and keeping in mind that the referral process should be based on sound casework principles.

It has been pointed out that the rehabilitation of an individual requires an assessment of the total person in order to determine his ability to utilize the various resources available to him. It is also important that the referral is seen as desirable by the patient and appropriate to his needs. The findings of this study indicate that in almost all cases a clear diagnostic understanding of the patient's problem was given in the Social Service record, with reference made to family factors, medical diagnosis, work history, and the reason for referral being clearly stated. The patient's participation in the referral was indicated and, in most cases, the feelings and motivation of the patient for referral were stated. In a few instances, information regarding the patient's work history, educational background and intelligence potential, all pertinent to rehabilitation, was limited, especially in regard to the length of time unemployed. This latter would seem of particular import in evaluating a patient's attitudes and motivation to work.

There was no indication that referrals were made merely as routine procedure, but rather the referrals were seen as an integral part of the casework process in which the major focus was on the service to the patient.

Knowledge of the functions and services of DVR seemed clear to the worker making the referral, as indicated not only in the reason for referral but also in the apparent appropriateness of the referral. It may be recalled that an appropriate

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**Social Service Department

referral was considered to be one in which the patient's needs and interests could be feasibly met by the services offered by DVR.

The follow-up study further revealed the apparent success of most of the referrals, a successful referral being considered as one that was appropriate and services provided in accord with the patient's needs and interests.

The effectiveness of a referral and the resulting service or lack of service to the patient may be related, to some degree, to the method in which the referral is made. It has been pointed out that the method of referral should be related to the nature of the problem and may consist of a phone conversation or a face to face conference. The importance of a confirming letter, including the medical problem, its social implications and the patient's interest and understanding of the referral, has been stressed. The findings of this study were not consistent with those of the other studies referred to, in that in this study the method most frequently employed was a phone call followed by a letter of confirmation, as opposed to just a phone call. No face to face conferences were found in the present study. It sohuld be noted, however, that this method (combination of phone call and a letter) was used in less than half of the referrals made, and this is consistent with the findings of the other studies. Such findings may or may not imply that the method of referral was related to the nature of the problem as the summary recording utilized by the Social Service Department does not permit an elaboration of the method and why it was used. It was noted, however, that the majority of referrals considered as successful did have referral letters.

The prompt and appropriate action taken on the referral by DVR would seem to indicate positive relations between the two agencies, clarity of purpose and co-ordination of service to the patient. However, it was found that in some instances there was a breakdown in communication between the agencies. This appeared not so much a lack of communication but rather inappropriate channeling of, and requests for, information between DVR and Social Service. As a result, it would appear that the actual teamwork was not as effective as it might have been. It has been stated that the Social Service Department acts as a liaison with other social agencies in regard to reports and the gathering of information. It is appropriate, therefore, that all communication from the DVR, on behalf of the patient, be directed to the Social Service Department.

The question arises in the writer's mind, however, as to the effectiveness of assessing inter-agency communication and the working relationships when the assessment is based only on reading case records. It would appear that much of the positive or negative inter-agency relationships result from the actual verbal com-

munication between agencies and is not necessarily indicated in the written word of the case record. It is therefore difficult to obtain a realistic picture of the relationships just from a study of the case records. Experience in this study shows that provision for verbal communication, by means of a questionnaire between the personnel of the two agencies, would have been useful.

Certain impressions can be derived as to the characteristics of this sample group of disabled persons referred for DVR services as there were certain similarities. All were under medical care at Henry Ford Hospital at the time of referral to Social Service and more than half of the cases (61%) were considered by the physician to be in need of vocational training and/or employment. All but one had a physical disability which appeared to be preventing gainful employment. The nature of the disability indicated a fairly high number (48%) of orthopaedic problems. This is consistent with the type of disability for which VR services are specifically designed. In all but a few cases, the patients had not had steady employment due to their disability, and all indicated financial hardship. The work history revealed work of an unskilled and semi-skilled nature.

There did not appear to be a significant correlation between the emotional factors involved and the outcome of the referral. It was found, however, that in most cases the reason for referral to DVR was consistent with the service provided.

As a result of the findings of this study, it would appear feasible that the following recommendations might be considered in terms of making service to the patient increasingly effective.

The referral procedures of the Social Service Department could be more closely adhered to in that all referrals are to be confirmed by letter including the reason for referral, the patient's feelings toward and understanding of the referral, the medical problem and its social implications. A written follow-up report should be requested by Social Service and all follow-up contacts with DVR by Social Service should be confirmed by letter. Case conferences are indicated when complex problems are being considered. Social Service should provide DVR with periodic medical reports, with the patient's permission, if the patient is accepted by DVR and under medical care at Henry Ford Hospital. Continuing collaboration between agencies is indicated if responsibility for total planning for the patient is to be shared. Social Service case records should include such pertinent factors necessary in assessing a patient for vocational rehabilitation as: work history and length of time unemployed; educational level and intelligence potential; and the presence of emotional factors of significance which may or may not complicate rehabilitation. On-going evaluation of the referral procedures and their effectiveness would seem indicated.

Table 1

DIAGNOSIS AND NATURE OF DISABILITY*

(At time of referral to Social Service which prompted DVR referral)

Diagnosis	*Number*
Diabetes	4
Emotional Disorders	4
Cerebral Palsy	3
Cardiac	3
Tuberculosis	3
Injury due to accident†	3
Amputation	3
Alcoholism	2
Post Polio	2
Mental Deficiency	1
Quadriplegia	1
Multiple Sclerosis	1
Bronchiectasis	1
Pyelonephritis	1
Bilateral Hearing Loss	1
Laryngectomy	1
Obesity	1
Total	35

*In several instances more than one diagnosis was given.

†Includes facial scarring, loss of hand function and bilateral femoral fractures.

THE PHYSICIANS' UNDERSTANDING OF SOCIAL SERVICE*

SISTER MARY LEILA KOEPPE, R.S.M., M.S.W.**

The purpose of this study has been to interview the chief physician of medical services and residents in order to determine their previous understanding of medical social services, their introduction to our department, their attitudes toward the services rendered, their utilization of the department, and to compile a list of suggestions for improvements in working relationships.

The method employed consisted of an investigation of pertinent literature, personal interviews with the physicians and a tabulation and analysis of their responses to seventeen questions contained in a previously prepared schedule. In addition to direct answers to the questions proposed, many of the physicians made valuable, additional comments.

In compliance with the duty imposed by specialization, impersonalization may result as the physician finds it necessary to keep pace with present world trends. This tendency can be prevented in only one way — the art of medicine and the science of medicine must truly learn to complement each other.[1] A review of the current medical picture today, indicates that the physician finds it increasingly difficult to carry on an on-going relationship with his patient, because frequently he does not have the time to devote to it that his patient requires or for countless other reasons that might be suggested.

The gap, indeed chasm created by this splitting of effort has come to be bridged by the field of social work, especially through the social service departments set up in hospitals. Thus, the value of social service departments, whose members are important in present day interdisciplinary approaches, is unquestionable. Here valuable relationships can be established and social services rendered that will ultimately spell greater success in the practice of good medicine. Consequently, it is vitally important for medicine and medical social work to strengthen their relationships in the hope that the enabling profession can be more helpful. We cannot afford to let specialization and impersonalization make us lose sight of the total patient; rather we must, in the words of Hubert Bonner, "be ready to take inventory of gaps in preparation for broader approaches to health services."[2]

In 1954, our Social Service Department was established. This department was unique from its very beginning because it has always employed full time, professionally qualified personnel. The social service department is just one unit of the total program in the hospital. Any services rendered by the department are a planned part of medical care. Social service is initiated by direct referral from the doctors and is specifically directed toward the inter-relationship of the medical and psycho-

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social factors in the over-all treatment of the patient. There is no doubt that social services play an intimate part in our medical program. This is as it should be because the physicians are vitally concerned with helping people with their personal problems in relationship to the health factors. The writer was impressed with the freedom, ease and frankness of the respondents and felt that this was indicative of a basic positive feeling between the two professions in this hospital.

The day is past — or it should be — when social services are considered as merely relief-giving agencies or as just a liaison between the hospital and the community agency. At present the term medical social service has a much broader connotation. Because of the broad understanding and close relationship between physicians and medical social workers, which is necessary to give total patient care, it seemed advisable to undertake a study of this nature.

The author considered it important to have some knowledge of the physicians' previous experience with medical social work as an aid toward a better understanding of their attitudes toward the utilization of this social service department. Consequently, the first three questions asked during the interview pertained to this phase of the problem. Judging from the twenty-five medical schools represented in this study and in reference to the graduation dates listed, there has been little exposure of the medical students to the full value of medical social services.

Physicians, like any other professional people, tend to make the most use of those services to which they have been properly oriented and of which they have a clear understanding. Table I shows the responses of the physicians regarding orientation to the social service department.

Table I

PHYSICIANS' AND RESIDENTS' ORIENTATION TO THE MEDICAL SOCIAL SERVICE DEPARTMENT

	Method of Orientation	Chiefs of Medical Services	Residents	Total
(A)	Ancillary product	1	1	2
(B)	Self-acquired knowledge	4	3	7
(C)	Administrative Announcement and talks from social service department personnel	28	2	30
(D)	Various contacts	2	2	4
	Total	35	8	43

UTILIZATION OF SOCIAL SERVICES BY PHYSICIANS

The next five tables illustrate the attitudes of the physicians toward and the extent to which they make use of the social service department.

Table II

REFERRAL OF PATIENTS TO THE SOCIAL SERVICE DEPARTMENT

Referral of patients to department	Chiefs of Medical Services	Residents	Total
A. Referrals			
Yes	23	5	28
No	2	2	4
Infrequently	10	1	11
Total	35	8	43
B. How initiated			
Consultation sheet	2	2	4
Phone	7	1	8
Personal contact	3	1	4
Worker on floor	1	2	3
Secretary makes contact	2	—	2
Weekly conference	1	—	1
Present system (combination)	19	2	21
Total	35	8	43

A cursory examination of Table II evidences that the physicians make good use of the services and use a variety of methods in making referrals.

Table III

OPINIONS OF PHYSICIANS CONCERNING THE SERVICES, REFERRALS AND SYSTEM OF COMMUNICATION IN THE SOCIAL SERVICE DEPARTMENT

	Chiefs of Medical Services	Residents	Total
A. Evaluation of services rendered			
1. Generally satisfied	27	6	33
2. Partially satisfied	2	—	2
3. Inability to answer	3	1	4
4. No answer	3	1	4
Total	35	8	43
B. Adequacy of present referral system			
1. Generally acceptable	27	3	30
2. Partially acceptable	5	4	9
3. No answer	3	1	4
Total	35	8	43
C. Communication desired			
1. Personal	14	2	16
2. Written	3	—	3
3. Social summary	2	3	5
4. Indifferent	9	1	10
5. Immediate — in emergencies	7	—	7
6. No answer	—	2	2
Total	35	8	43

Table III reveals three aspects of the physicians' attitudes towards social services. The majority of the physicians are satisfied with the services rendered by the department and consider both the coverage of their cases and the present referral system adequate. Most of them prefer personal contact with the department after the referral is made, because they believe it makes for better understanding and helps to avoid possible difficulties.

Table IV

FORTY-THREE PHYSICIANS' OPINIONS CONCERNING FEE-FOR-SERVICE CHARGES BY THE SOCIAL SERVICE DEPARTMENT

Opinions	Chiefs of Medical Services	Residents	Total
Yes	28	6	34
No	6	2	8
Doubtful	1	—	1
Total	35	8	43

Table IV summarizes the physicians' opinions relative to charging a fee for social service. Most of the doctors are in favor of a fee-for-service charge by the department provided that there is flexibility. On the other hand, some doctors hesitate to use the consultation sheet because of the definite fee-for-service charge in this particular instance.

The questions pertaining to the reading and use of the social summary sheet, the value they attribute to them, their adequacy, and the extent to which they consider them contributory to total patient care provoked many interesting and varied comments. The results of this part of the interview, together with whether or not the data contained in the social summary sheet would modify patient management, is recorded in Table V.

Table V

OPINIONS EXPRESSED BY FORTY-THREE PHYSICIANS CONCERNING THE SOCIAL SUMMARY SHEET

Responses of Physicians	Chiefs of Medical Services	Residents	Total
A. Summary sheet read by physicians			
Yes	27	6	33
No	5	1	6
No answer	3	1	4
Total	35	8	43
B. Valuable to patient and physician			
Yes	27	6	33
No	1	1	2
Doubtful	5	1	6
No answer	2	—	2
Total	35	8	43
C. Modification of patient management			
Yes	28	7	35
No	1	—	1
Doubtful	2	1	3
No answer	4	—	4
Total	35	8	43
D. Adequacy			
Yes	21	3	24
No	2	—	2
Doubtful	3	1	4
No answer	9	4	13
Total	35	8	43

The social summary sheet is read by most of the physicians. They consider the data in it both adequate and valuable. However, many of them think there should be revision in the way in which it is written so that its contents will be more concise, simplified, and not contain confidential and psychiatric information. Many physicians claim that they frequently modify patient management after reading the social summary sheet. On the other hand, there is still evidence of misconceptions concerning the scope and functions of the social service department and of limited perspective on the part of many of the physicians — of specialists in particular.

Fourteen physicians favor attendance of workers at case conferences; whereas, only eight would even consider the possibility of having them accompany physicians on ward rounds. They can visualize patients, physicians, and workers profiting from the inclusion of medical social workers at certain case conferences; but they believe that their attendance on ward rounds might easily lead to confusion and result in a waste of time for both physicians and workers.

Physicians' Suggestions Pertaining to the Henry Ford Hospital Social Services

A number of physicians made several valuable contributions which can be classified under three major categories as follows:

A. Case Workers:

1. Inexperienced workers must be made to understand their limitations, otherwise embarrassing situations can result.
2. A correct understanding and realization of their true role, on the part of medical social workers, will tend to establish better doctor-worker relationship.
3. There is a definite need for more selectivity in the personnel. Case workers should be more personable, more imaginative, but dignified, and of a high caliber.

B. Social Service Department

1. A better orientation program to the department should be provided for both staff physicians and residents. Such a program would enable them to see its value and the possibilities of including social workers as team members.
2. The role and function of the social service department should be included in the hospital's medical handbook.
3. Brochures and other publications should be issued by the department to acquaint the physicians with the scope of medical social services — the problems handled, the specific ways it can help them, and the variety of services offered.
4. Lists of community resources should be prepared and distributed by the department.

5. Provision should be made for more consultations between physicians and medical social workers.
6. There is a need for greater concentration on the true professional status of medical social services, regardless of the time, effort and finances involved.
7. Greater effort should be made to convince physicians of the need for earlier referrals in order to relieve prolonged patient stress.
8. Provision of a check list of problems handled by the department for use by the physician when making referrals.
9. A periodic circular of available services offered by the department to patients.
10. Frequent dissemination of information concerning the department's accomplishments will result in a better understanding of its value to patients and physicians.
11. Social summaries should be more concise and more orderly.
12. There should be more action and less detailed paper work.
13. Revision of present consultation sheet by adding medical social services.
14. Greater involvement in home casework would be beneficial.

C. The Profession of Social Work

1. There is a definite need to elevate the whole field of social work to a professional status.
2. Provisions should be made to eliminate the current narrow conception of the field of social work as merely a financial agent, even to the extent of changing the name if necessary.

Conclusions and Recommendations

The following statements, based upon data obtained from the personal interviews in the present investigation, are offered by way of conclusions and recommendations:

1. According to the present study, a definite need for more training and orientation to social services in medical schools is indicated. Continued research in this area is needed.
2. Provisions should be made for proper orientation of interns and residents to the social service department; for example, lectures for each incoming group. Moreover, some type of follow-up should be provided to continue their interest in and awareness of social services; for example, brochures, monthly reports and other publications by the department.
3. Many physicians do not have a sufficiently comprehensive knowledge of medical social services. Many tend to consider the department primarily

as a financial agent or a liaison for community resources only. Collaborative reasearch in the role and functions of medical social services by physicians and medical social workers might answer this problem.

4. The status of the social-work profession might be elevated through greater selectivity of incoming students. Possibly national criteria and screening tests determined by the Schools of Social Work and the Council on Social Work Education similar to that of the nursing profession, should be undertaken.

5. Social summaries should be more concise, have simpler terminology, and represent a social, diagnostic evaluation. There is a definite need for research in the method of writing medical social summaries.

6. The present study affords a sound basis for further research. It is urgently recommended that similar investigations be made in other hospitals having social-service departments and the results be pooled, compared and analyzed to determine further needs.

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2. Bonner, H.: Social Psychology: An Interdisciplinary Approach, New York, American Book Co., 1953, p. 349.

COMBINED ACTION OF 5-FLUOROURACIL AND OTHER CYTOTOXIC AGENTS WITH CRYSTALLINE RIBONUCLEASE ON MOUSE ASCITES TUMOR†

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(With the technical assistance of Zinaida Lashischenko)

As Brachet[1,2] has emphasized for many years, cytoplasmic ribonucleic acid (RNA) is of fundamental importance to life and is now generally believed to be the blueprint or template directly involved in the synthesis of the body's enzymes. The RNA somehow directs the correct number of the specific amino acids into the proper sequence to form the protein chain or chains of the enzyme. It, in turn, is probably constructed according to directions from the nuclear desoxyribonucleic acid (DNA). Although some believe that DNA (location of genes) is capable of duplicating itself, ribonuclease (RNase) treated protoplast cannot resynthesize DNA.[3] Roth[4] has detected an increase in desoxyribonuclease (DNase) activity in cells incubated with crystalline RNase, suggesting a degradative function of the latter enzyme. Nucleolar RNA is quantitatively greater in all malignant cells.[5] Taylor and Long[6] have noted up to 70 times greater RNA content of Grade III ovarian and endometrial neoplastic nucleolar cores as compared to Grade I.

Migliarese[7] reported an increase in RNase activity associated with the growth of certain tumors in man and animals. Other workers[8] have shown an elevation of serum RNase in 71% of patients with cirrhosis and 62% of leukemic patients, but in only about 30% of patients with carcinoma or Hodgkins disease. It is of great interest that ribonuclease has been reported to demonstrate strong anti-mitotic and growth-inhibiting effects on sea urchin eggs,[9,10] living amoebae,[11] onion root tips,[12-14] salamander eggs,[15] cells in tissue culture[16] and cells synthesizing tobacco mosaic virus,[17] as well as certain experimental tumors.[18-22] There is even a report of RNase causing a temporary remission in chronic myelogenous leukemia.[23]

Perhaps the most significant finding has been made by Ledoux who found that RNase was capable of producing regressions of spontaneous mammary tumors in C_3H mice,[20] which are unusually refractory to chemotherapy. However, other workers found the drug ineffective in these cases.[24] For the past six or seven years Ledoux has been emphasizing the importance of ribonuclease in tumor therapy. He has received some criticism because of the well known heterogenous nature of RNase, as well as the fact that the bovine pancreatic enzyme he worked with has a much smaller molecular weight than intracellular RNase's.

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†Drugs used in this study were obtained as follows: 5-Fluorouracil was supplied by Dr. William Wilson, formerly, Chief, Cancer Chermotherapy Section, Hahnemann Medical College and Hospital, Philadelphia, Pa. Glucose-1-Phosphate hydrazine and Polyphosphate were prepared and supplied by Dr. Cardenas. 9-B-D Psicofuranosyl adenine was supplied by Dr. James Lawson, Upjohn Co., Kalamazoo, Michigan.
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We have been extensively studying the action of RNase on experimental tumors. This communication records the effects on Ehrlich ascites tumor of RNase in combination with other agents reported to have a cancer chemotherapeutic effect. The drugs were: 5-Fluorouracil (5-FU);[25-30] Glucose-1-phosphate hydrazine (G-1-P-H);[31,32] 9-B-D psicofuranosyl adenine (psicofuranine);[33-35] or condensed polymerized phosphate chains.[36,37]

These drugs were selected for a variety of reasons. 5-FU is a fluorinated uracil and a pyrimidine antagonist which is incorporated into ribonucleic acids.[38] In man the drug's highest concentration is found in the RNA of tumors and intestinal mucosa.[30] It can prevent thymine synthesis by inhibiting thymidine synthetase[39] and blocks uracil phosphatase so that preformed uracil cannot be utilized in RNA synthesis.[40] G-1-P-H demonstrates a cytotoxic action presumably because of its hydrazine group. The metabolic itself has been reported to be taken up selectively by tumor cells.[41,83] Psicofuranine was recently developed as an antibiotic effective against M. aureus and E. coli and produced by a strain of actinomycete identified as *Streptomyces hygroscopicus* var. *decoyicus*.[42] It is unusual in that it is an abnormal ribonucleoside in which the sugar moiety (6 carbon sugar with pentose lactone linkage), rather than the heterocyclic base, has a structural defect. The drug inhibits the formation of guanylic from xanthanilic acid.[43] Polyphosphate chains inhibit several enzyme systems *in vitro* by competitive inhibition or by sequestrating cations (Ca^{++} and Mg^{++}).[37] They may interfere with high energy phosphate systems *in vivo*.

MATERIALS AND METHODS

Sarcoma 37 ascites tumors were maintained in adult female Swiss white mice averaging 25 grams in weight by weekly inoculation of 0.2 ml. of cell suspension. After such intraperitoneal (I. P.) injection of fresh ascites fluid, the mice regularly develop large amounts of milky ascites (5-15 ml.) in 6-12 days and die in 10-15 days. These transplantable cancers have 100% "takes" and rarely show spontaneous regressions.

The RNase used was 5x recrystallized bovine pancreatic ribonuclease purchased from Sigma Chemical Company. The mice were separated into several small groups (10 controls and 10 experimentals, each). All experimental animals received 2 mg. RNase (80 mg/kilo) I.P. daily for a week after the tumor had been established 24 hours (days 1-8). The other drugs were administered in a similar manner on the same days as separate injections. 5-FU was only given on days 1-6. Polyphosphates were prepared by dehydration of mixtures of monosodium and disodium orthophosphate.[44] The maximal chain length was 67 phosphorus atoms. Doses used were:

5-FU	0.5 mg/day	(20 mg/kilo)
G-1-P-H	2.0 mg/day	(80 mg/kilo)
psicofuranine	8.0 mg/day	(320 mg/kilo)
polyphosphate	1.0 mg/day	(40 mg/kilo)

All drugs were administered through a Swinney filter adapter to assure sterility. Antibiotics were not used. Diet was Purina Laboratory Chow and tap water supplied ad libitum. The mice were maintained in air conditioned quarters (74°F).

RESULTS

In previous studies,[45-47] we reported that 4-5 mg. crystalline RNase (Sigma) given intraperitoneally daily 24 hours after an ascites tumor was established, prolonged the survival time by a factor of two. While the effect of a 2 mg. dose was variable in this respect, it nevertheless produced the same marked alteration in 8 day tumor cytology seen with the larger doses. One mg. doses had no effect. Although combinations of total body x-irradiation plus I.P. RNase (i.e., 2 mg. RNase daily plus 600r, day 2) seemed to have a synergistic effect in that survival time was further prolonged, the tumor total packed cell volume was not inhibited to the degree seen with 4-5 mg. RNase alone. A finding of perhaps greater significance is an apparent radiation protective effect of the enzyme. Mice which had received doses of ionizing radiation which were 100% lethal to the controls, lived either long enough to die from their transplanted cancer, or even longer.

Although there was quite a bit of variation in different trials using 2 mg. RNase alone, the average survival time of these animals in the various groups was 18.1 days (controls = 13.6 days). The results in the combination therapies are shown in Table I. Ribonuclease plus 5-FU gave the most interesting findings, with a prolongation of survival period to 2.5 times control (Fig. 1). Total body weight changes, which are felt to reflect tumor growth, are shown for the controls and for this group in Figs. 2 and 3.

There was some weight loss at these doses, but no deaths due to 5-FU toxicity. When therapy was stopped after the first week the weights returned to

Table I

SUMMARY OF COMBINATION THERAPY EFFECTS. 10 MICE IN EACH CONTROL AND EXPERIMENTAL GROUP. (DOSES: RNase, 2 mg/day; 5-FU, 0.5 mg; G-1-P-H, 2 mg; psicofuranine, 8 mg; polyphosphate, 1 mg)

Therapy (Daily injections, Days 1-8)	Average Survival Time (Treated/Control)	Average Weight Change/Day (T/C)
Ribonuclease alone	18.1/13.6 days	+0.15/+0.74 g
5-Fluorouracil + RNase	32.5/13.4	−0.01/+0.79
Glucose-1-Phosphate Hydrazine + RNase	20.2/13.3	+0.31/+0.83
Psicofuranine + RNase	16.5/13.9	+0.39/+0.81
Polyphosphate + RNase	14.5/13.6	+0.71/+0.91

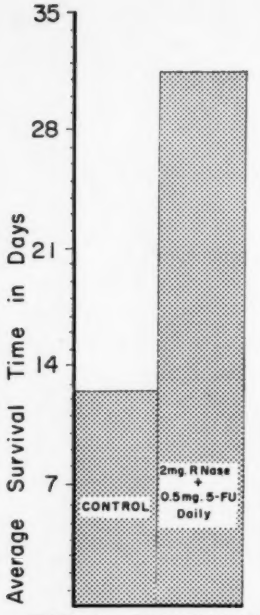

Figure 1

Prolongation of survival time by intraperitoneal therapy with ribonuclease plus 5-fluorouracil.

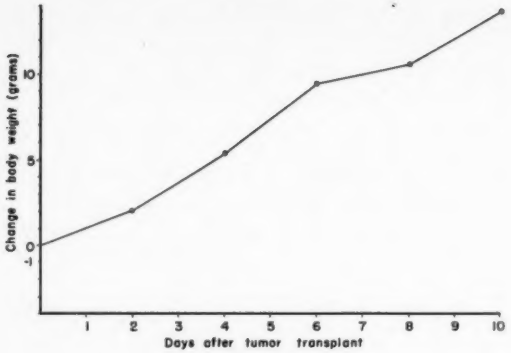

Figure 2

Average weight gain in control mice with ascites tumor.

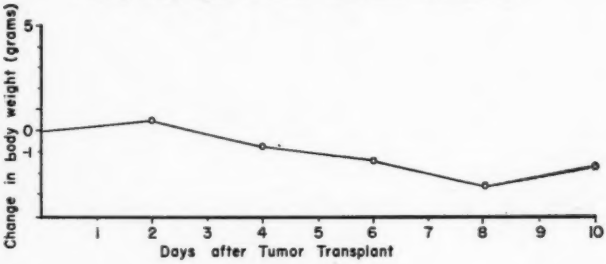

Figure 3

Average weight change in tumor-bearing mice treated with RNase plus 5-FU.

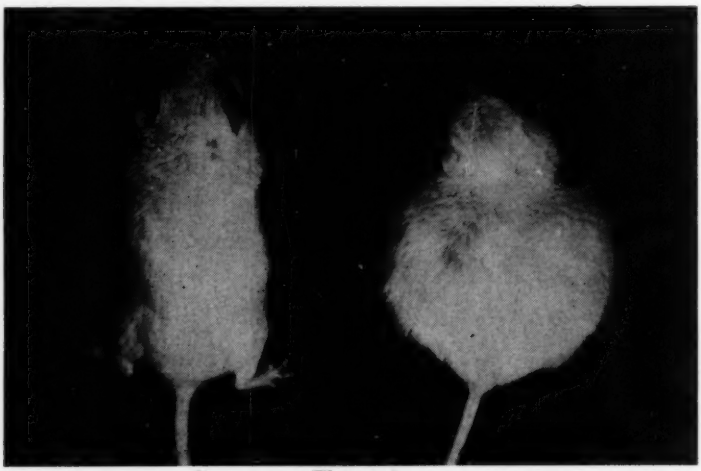

Figure 4

Control mouse (right) and one with identical tumor transplant, but treated with 2 mg. RNase plus 0.5 mg. 5-FU, daily. (13 days after tumor inoculation.)

pre-treatment levels and thereafter increased very little. Half of these animals showed no sign of ascites tumor or solid tumor. Some of these animals were alive 6-7 weeks after tumor transplantation, before starting to show some emaciation and succumbing to solid abdominal wall and peritoneal malignancies. The other 50% had a striking generalized carcinomatosis that was first seen at the third week in sacrificed animals. There were numerous discrete masses of tumor infiltrating the peritoneal tissues, especially the omentum and epiploons, as well as the chain of ganglia and lymph nodes. Parenchymatous organs such as the kidneys and liver were also often involved by single or multiple whitish gray nodules of a rubbery consistency and a small cystic surface on cut section. Cells were similar

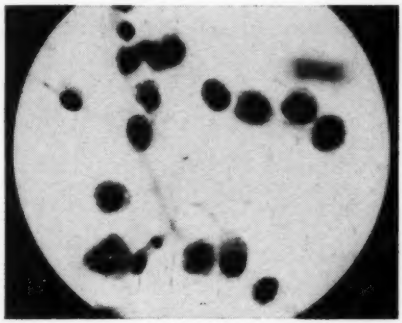

Figure 5a

Typical smear from a malignant ascites tumor.

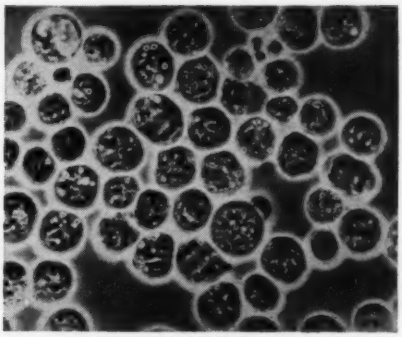

Figure 5b

Phase photomicrograph of a control smear, showing several cells in active division. (Courtesy of Dr. Jens Christensen)

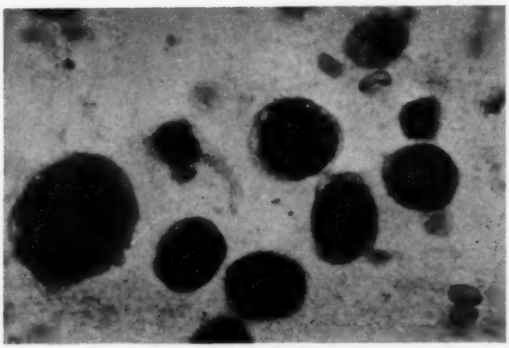

Figure 5c

1280 x enlargement of control smear. Several erythrocytes are also seen. Papanicalaou stain. (Courtesy of Dr. Irena Kowprowski)

to those of the original inoculum. Supra-diaphragmatic viscera showed a similar picture, as did lymph nodes (cervical, mediastinal and inguinal). Occasionally jaundice was seen when tumor involved the biliary tree. Several new solid tumors were detected in the subcutaneous tissues of the back.

Nothing unusual was noted with the other drugs, except that glucose-1-phosphate hydrazine had a similar or slightly synergistic effect with RNase. Psicofuranine or polyphosphate had no effect or inhibited RNase action.

Inoculation of experimental animals with malignant cells in which RNA content has been reduced by storage at 4°C is much less effective in producing tumor "takes" than inoculation with fresh cells.[48] Simultaneous administration of RNA causes an increased number of tumors.[49] When normal rat liver cells are treated with RNA from malignant liver cells and then inoculated I.P. into rats, 20% develop tumors whereas none did when normal liver RNA was added.[50] However, Niu[51,52] found RNA effect to be related to dose. In physiologic concentration it could produce differentiation of young urodele gastrula, while very large doses actually prevented further growth of the embryo or transplantation I.M. of ascites cells (incubated with normal mouse liver RNA).[51]

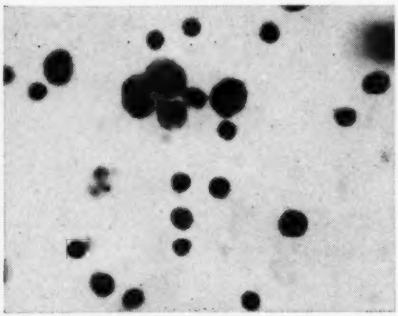

Figure 6a

Smear from animal treated with RNase plus 5-FU. Many of the cells are smaller than usual. Effect is similar to that seen with RNase alone.

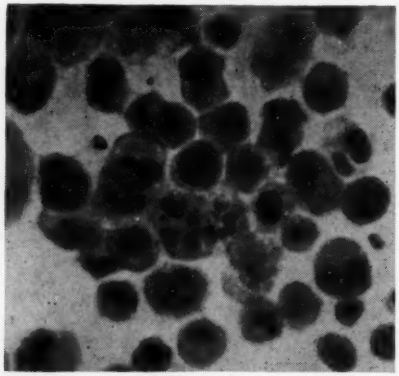

Figure 6b

Smear from animal treated with RNase plus polyphosphate. No great morphological alteration.

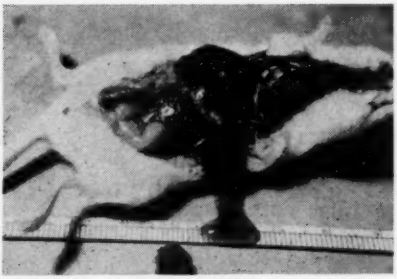

Figure 7

Animal sacrificed 28 days after Sarcoma 37 injection, and treated for one week with RNase and 5-FU. Note minimal amount of viscous ascites. Spleen is riddled with small solid tumors and several were present in the mesentery.

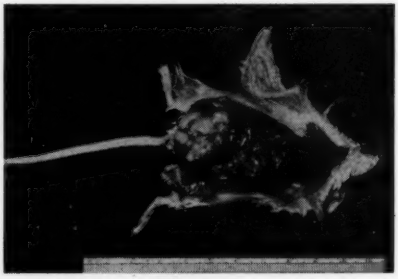

Figure 8

Animal sacrificed 28 days after tumor inoculation, treated with RNase plus 5-FU, showing large solid tumor filling lower abdomen and matting together much of the viscera. This tumor, as well as all of the animal's subcutaneous tissues and sclerae, was intensely icteric.

DISCUSSION

DeCarvalho and Rand[50] have reported a modification of rat Novikoff hepatoma growth by treating the cells with RNA from other hepatoma cells prior to transplantation. A much more widely disseminated neoplastic picture with unusual widespread metastases was seen, although prior treatment of the controls with normal rat liver RNA caused no such alteration. Despite the more malignant growth pattern of the former, some regressions were seen, although none were seen with the controls. Their description is quite similar to the RNase + 5-FU effect on some mouse ascites tumors. While it is conceivable that one or two of the solid tumors may have developed spontaneously, it is highly doubtful that all of them did.

Although RNase and G-1-P-H have a more beneficial effect when used together, it is not an additive one. While we feel that the action is due to a cytotoxic effect of the hydrazide, it is quite possible that the compound is a specific antagonist. Thus, D-glucosamine, a competitive inhibitor of glucose for hexokinase, inhibits both Sarcoma 37 and human epidermoid carcinoma in tissue culture.[53,54]

Extensive studies with polyphosphates on solid and ascites mouse tumors showed that they were ineffective in these animals, perhaps due to a species specific enzyme. The loss of the usual RNase effect when the drugs were used together may have been due to inactivation of the enzyme by phosphorylation which occurs even with a single phosphorus atom.[52] There has been at least one definite temporary

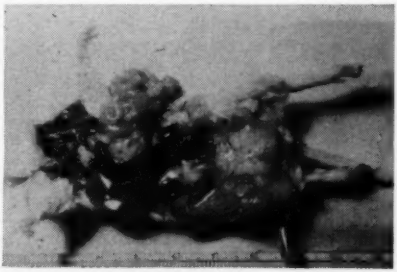

Figure 9

Autopsy 35 days after tumor transplant and treatment (RNase plus 5-FU), showing solid mesenteric tumor with isolated hepatoma. Latter has a smaller neoplasm near it.

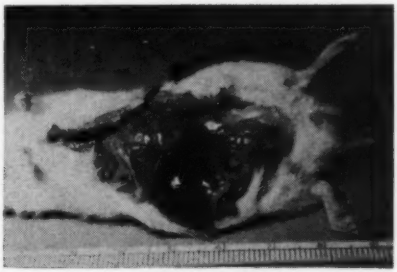

Figure 10

This animal represented another clinical "cure" but showed a small amount of bright yellow ascites plus multiple liver metastases when it died. A solitary left renal tumor was also present.

remission, both clinically and hemotologically, in a patient with leukemia on polyphosphate.[31] A tendency to hypocalcemia and even tetany is a significant toxic effect. At Henry Ford Hospital three terminal cancer patients were given polyphosphate in daily intravenous drips for 60 minutes at doses up to 600 mg. (8 mg/kilo).[55] No effect, including any change in serum calcium, was seen.

We were able to confirm the lack of chemotherapeutic action of psicofuranine on the Ehrlich tumor. When used with RNase, the biological effect was similar to that obtained only with the latter treatment. Because of its unique structure, psicofuranine has had extensive clinical trials, but antitumor activity at non-toxic

doses was negligible. An unusual syndrome produced is polyserositis, especially pericarditis.[56-58,68] Nine of 12 patients at this institution developed the fullblown picture of fever, mental confusion, moderate leucocytosis and severe chest pain with audible pericardial friction rub.[57] Symptoms subsided when the drug was discontinued and returned upon readministration. In some the picture resembled the Periodic Disease originally described by Reimann,[59-61] later referred to as Familial Mediterranean Fever[62] and recently renamed by Nixon and Priest[63-65] as Familial Recurring Polyserositis.

Ledoux[20] estimated that the Armour beef pancreas RNase he used in retarding C_3H mice spontaneous mammary tumor growth contained 25-30% of fully active

Figure 11a

28 day tumor treated with RNase plus 5-FU for one week after tumor transplant. Solid tumor in lower abdomen.

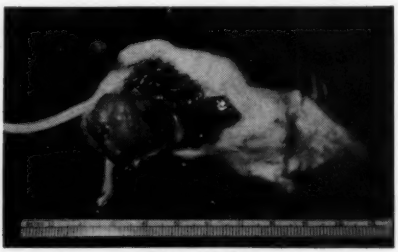

Figure 11b

Mass uncovered. It involves the ventral peritoneum. No ascites was present.

enzyme and 70-75% of inactive low molecular weight RNase. There was an impression that the inactive portion could inhibit the active one. He found that two intraperitoneal injections (days 7 and 8) of 2 mg. Armour RNase purified by chromatography (peak "D", the largest peak) *plus* 0.1 mg. nucleotide almost tripled the survival time of a group of ascites tumors.[19] Other doses when given without nucleotide or even 10-20 mg. doses of unpurified enzyme, had a less beneficial effect. Extensive studies[21,66,67] have led him to believe that the cancerocidal

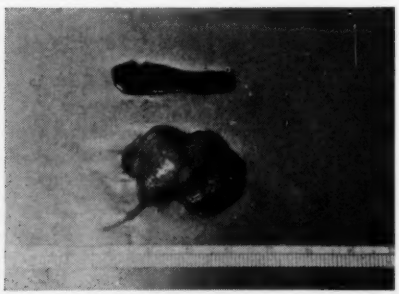

Figure 11c

The tumor dissected out. Above is the animal's spleen, which was larger than normal.

Figure 11d

Section of the tumor (hematoxylin and eosin, 175x). It is composed of closely packed cells of a type similar to those of the original inoculation.

effect of RNase is due to the rapid synthesis of a new and abnormal cellular RNA, rich in pyrimidine bases, which somehow initiates cellular alterations and a steady decrease in RNA.

RNase is frequently reported to be present in the cytoplasmic mitochondria.[69] Recent workers have shown that it is actually located in cytoplasmic particles called "lysosomes",[70] which may contaminate mitochondral fractions. It has been shown that rat liver RNase has two peaks of activity, one at acid pH and another at alkaline pH.[71,72] Roth has noted that an RNase inhibitor is normally present in the rat liver,[73] and has recently described a third rat liver RNase which is bound to this inhibitor and found in the supernatant fraction.[74] The optimum activity of the enzyme occurs at the same pH, whether in solution or adsorbed to a surface.[75]

An important report made earlier this year concerns a ribonuclease inhibitor which has been isolated from Ehrlich ascites tumor cells.[76] This has been shown to inhibit bovine pancreatic RNase and could possibly play a role in these chemotherapeutic trials. Bivalent ions such as Mg^{++}, Mn^{++} and Cu^{++} all inhibit RNase attack on rat microsomal ribonucleoprotein.[77] Several polyionic compounds, especially polymethacrylic acid, reverse RNase inhibition of protein synthesis.[78] Many workers have uncoiled the chain of 124 amino acids that make up RNase by breaking disulfide bridges but not the chain itself, so that the enzyme is inactivated. This process is reversible and thought to be a mere "uncoiling" rather than true denaturation because reactivation of RNase can be brought about by proper conditions. Thus the compound refolds under the influence of RNA, if there are polyvalent anions in the substrate, even in the presence of strong agents like 8 M urea or 1 to 3 M solutions of guanidium ions.[79] Activity of reduced and modified RNase is also restored by the presence of molecular oxygen and suitable alkalinity.[80,81]

SUMMARY

Ribonucleic acid is directly involved in the synthesis of most of the important enzymes and proteins, under physiological conditions. There is gorwing opinion that the riddle of cancer may lie in some abnormality of nucleoprotein metabolism, especially of RNA. Important work has been performed and frequently reported by Ledoux on ribonuclease action against various experimental tumors. We have confirmed some of these studies and extended the work. Other workers have had difficulty in reproducing his results, although Ledoux himself has reported a variation of biological effect with different sources and lots of crystalline bovine pancreatic RNase.

In the present experiments crystalline RNase was used in combination with several other drugs in the mouse Sarcoma 37 ascites tumor. Two of the agents, glucose-1-phosphate hydrazine and polyphosphate, were prepared in our own laboratories. The other drugs were an abnormal nucleoside, 9-B-D psicofuranosyl adenine, and 5-fluorouracil. Intraperitoneal injection of 2 mg. RNase daily (days 1-8) and 0.5 mg. 5-FU daily (days 1-6) resulted in a prolongation of average survival time 2.5 times that of the controls (32.5 compared to 13.4 days). Furthermore, steady weight gain as a manifestation of tumor growth was not seen in the treated mice. Half of them never developed any ascites tumor but died within six weeks

with large solid abdominal wall and peritoneal tumors. The other 50% had an unusual widespread carcinomatosis that was first detected three weeks after original transplant. Solid tumor involved all of the peritoneal and omental tissues, as well as liver, kidneys, heart, cervical, mediastinal and inguinal lymph nodes, and subcutaneous tissues of the back. Jaundice was sometimes seen. Peritoneal smear six days after tumor inoculation showed numerous small round cells with minimal cytoplasm and some nuclear pycnosis. Occasional typical ascites tumor cells were seen.

Glucose-1-phosphate hydrazine plus RNase produced a survival time of 20.2 days, which was slightly greater than with the enzyme alone. Psicofuranine had no additive effect and polyphosphate seemed to reduce the usual RNase effect. Ascitic smears from an 8 day animal of the latter group failed to show any unusual cytological changes.

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INTRODUCTION OF NEW STAFF MEMBERS

JOHN V. BALIAN, M.D., returned as a Staff Member to the Henry Ford Hospital Ophthalmology Department on July 10, 1961. He was born in France on December 26, 1928 and received his premedical as well as medical training at Wayne State University. He obtained his A.B. in 1951 and M.D. in 1955. Dr. Balian interned at Wayne County Hospital. From 1956 to 1959, he was a Resident in Ophthalmology at the Henry Ford Hospital. As a Captain in the Army and Chief of the E.E.N.T. Service, he spent the next two years at Fort Campbell, Kentucky. Dr. Balian is a Diplomate of the American Board of Ophthalmology. His home address is 21520 Cambridge Street, Detroit, where he lives with his wife, Annette, and four children.

RALPH E. BAUER, M.D., became a member of the Anesthesia Staff in September 1961. He is a native of Portsmouth, Ohio, where he was born on August 25, 1930. In 1952, he received his B.A. from Ohio Wesleyan and in 1956, his M.D. from the University of Cincinnati College of Medicine. After interning at the Henry Ford Hospital, he became a Resident in Anesthesia from 1957 to 1959. Dr. Bauer was a Lieutenant in the Navy at Camp Pendleton, California for two years, serving as Chief of the Department of Anesthesia. He is a member of the American Society of Anesthesiologists and a Fellow in the American College of Anesthesiologists. He lives with his wife, Nancy, and one child at 13942 Warwick in Detroit.

GEORGE C. BOWER, M.D., joined the Division of Pulmonary Disease July 1, 1960. He is from Galesburg, Illinois and was born December 7, 1926. He attended Knox College, Stanford University, and received his B.S. from Northwestern University in 1947. Dr. Bower interned at Cook County Hospital in Chicago after obtaining his M.D. from Northwesten University in 1950. He was a Resident in Medicine at the University of Colorado Medical Center and was Chief Medical Resident from 1956 to 1957. From 1957 to 1960, Dr. Bower held a National Tuberculosis Association Fellowship and was a member of the Colorado Foundation for Research in Tuberculosis. He was also a consultant in pulmonary disease to the Colorado State Hospital from 1958 to 1960. George and Virginia Bower live with their three children at 458 Belanger in Grosse Pointe Farms.

MAX D. CLARK, M.D., became a Staff Member of the Department of Radiology July 1, 1960. Born in Walkerton, Indiana, December 13, 1928, he received his PH.D. from the University of Chicago in 1948 and his M.D. from Indiana University Medical School in 1956. Dr. Clark interned at the Presbyterian St. Luke's Hospital in Chicago and was then a Resident in Radiology at the Henry Ford Hospital from 1957 to 1960. He was in the Army Medical Battalion at Fort Lewis, Washington from 1948 to 1949 and was at the Army Hospital Laboratory at Camp Atterbury

in Indiana from 1950 to 1951. He is a member of the American Board of Radiology. His home address is 2631 Woodside Drive in Dearborn, where he lives with his wife, Mary, and two children.

BEVERLY A. COLLIER, M.D., joined the Department of Anesthesiology Staff on July 1, 1960. She was born in Evansville, Indiana May 20, 1933. After graduating from the University of Toledo with a B.S. degree in 1953, Dr. Collier obtained her M.D. from the Ohio State University School of Medicine in 1957. She then interned and took her Anesthesia Residency at the Henry Ford Hospital. Dr. Collier is a member of the American Society of Anesthesiologists, the Michigan Society of Anesthesiologists and holds a fellowship in the American College of Anesthesiologists. She lives with her husband, Richard, at 2800 West Grand Boulevard in Detroit.

WILLIAM R. FELLOWS, M.D., came to the division of Allergy July 1, 1960. Born March 17, 1930 in Windsor Ontario, Dr. Fellows took his undergraduate and medical training at the Queens University School, receiving his M.D.C.M. in 1955. He was also Chief Resident at Rockwood Ontario Hospital in Kingston from 1951 to 1955. After an internship at Presbyterian Hospital in Chicago, he took his Medical Residency at the Henry Ford Hospital, spending his last year in immunology and renal disease. He belongs to the Ontario Medical Association. Dr. Fellows and his wife, Carol, have two children. Their address is 26685 Rouge River Drive in Dearborn.

HENRY H. GALE, M.D., joined the Division of Cardiovascular Disease July 1, 1960. He was born in Vancouver, British Columbia May 3, 1929. In 1950 he receiver his B.A. and in 1954, his M.D. degree from the University of British Columbia. Dr. Gale took his internship and residency at the Henry Ford Hospital. In his last year, he specialized in cardiology and cardiac catheterization. Dr. Gale, in 1960, became a Fellow of the Royal College of Physicians of Canada. His present address is 2400 Ewald Street in Detroit.

JAMES E. GARMAN, M.D., is a member of the Department of Radiology, having joined the Staff July 1, 1961. Born in Britt, Iowa, November 17, 1931, he received his B.A. degree in 1952 and his M.D. degree in 1955 from the University of Iowa. He interned at the Iowa Methodist Hospital in Des Moines. From 1956 to 1958, Dr. Garman was a Captain in the Army serving as a Battalion Surgeon in Europe. His residency in Radiology was completed at the Henry Ford Hospital. He, his wife, Evelyn, and two children live at 18900 Audette Street in Dearborn.

ABSTRACTS OF RECENT PUBLICATIONS OF THE PROFESSIONAL STAFF OF THE HENRY FORD HOSPITAL AND THE EDSEL B. FORD INSTITUTE FOR MEDICAL RESEARCH

STUDY OF THE DEFECTS IN THE BLOOD COAGULATION MECHANISMS IN POLYCYTHEMIA VERA. J. P. ABRAHAM, O. N. ULUTIN, S. A. JOHNSON, AND M. J. CALDWELL. Am. J. Clin. Path. 36:7, 1961.

From our findings, we suggest two newly studied causes of bleeding in polycythemia vera; the deficient content of factor three in the platelet and the friability of the clot quantitatively demonstrated in the fall-out phenomenon. These two abnormalities may or may not be related to one another. It seems very possible that the poor clot formation which results in the loss of red cells from the clot may be owing to the inadequate prothrombin-accelerating property of these platelets; however, to date, it has been impossible to demonstrate, by means of experiments, a relation between these two abnormalities.

HAZARD OF IATROGENIC PNEUMOTHORAX IN CERTAIN DIAGNOSTIC AND THERAPEUTIC PROCEDURES. R. O. ANTONI, AND J. L. PONKA. Surg., Gynec. & Obst. 113:24, 1961.

The detection of 76 cases of iatrogenic pneumothorax at Henry Ford Hospital between 1955 and 1959 indicates that this complication is not rare. The surgeon and the anesthesiologist should be alert to the possibility of its occurrence in all operations in and around the neck and thoracic cage. The possible mechanisms of production are reviewed. Unexplained respiratory distress or deterioration of cardiovascular dynamics in association with mild respiratory difficulties during the operative procedure, or during the postoperative period, should immediately arouse suspicion of pneumothorax, and immediate steps should be taken to establish the diagnosis and institute therapy. A suspected clinical diagnosis may be confirmed by bilateral thoracentesis since waiting for a roentgenologic diagnosis may be disastrous. Simple aspiration of air from the pleural cavity is frequently adequate as a method of treatment for this complication, since most cases are of the tension type. Prompt treatment by the establishment of continuous underwater drainage is essential to avoid severe morbidity and mortality in patients with disturbed cardiopulmonary function caused by the presence of air in the pleural cavity. There were no deaths in this series of cases.

DEATHS AND ILLNESS FROM BRONCHITIS, EMPHYSEMA, AND ASTHMA. G. BOWER. Am. Rev. Respirat. Dis. 83:894, 1961.

Standardized definitions for chronic bronchitis, pulmonary emphysema, and bronchial asthma do not exist. Emphasis in Great Britain is on chronic bronchitis

as the initial disease, with emphysema a complication. In the United States, emphysema is often considered a disease *sui generis*. Asthma is a term applied to a variety of conditions. Data from certain studies indicate that a large number of persons in the United States are subject to obstructive lung diseases of various degrees of severity. The crude death rate in the United States for chronic bronchitis, emphysema, and asthma combined has shown a steady increase since 1948. Death rates for emphysema and asthma in persons past middle age have shown a considerable increase between 1945, 1950, and 1955. The possibility that these diseases are causing more and more deaths (and disability) makes it important to have standardized terminology relating to them, and points out the need for further epidemiologic studies in this field.

EFFECTS OF PREDNISONE AND CORTICOTROPIN ON GASTRIC SECRETION: EXPERIMENTS IN HEIDENHAIN POUCH DOGS. L. Chaikof, W. H. Janke, P. C. Pesaros, J. L. Ponka, and B. E. Brush. Arch. Surg. 83:32, 1961.

The administration of 25 mg. prednisone orally caused an increase in the gastric secretion, and in free and total acid in Heidenhain pouch dogs. The average increase in free HCl secreted in 24 hours was 130%. The administration of 10 mg. prednisone orally also caused a similar increase, but to a less extent on the gastric secretion. Only 50% showed a significant increase in the free acid. The average increase in free HCl secreted in 24 hours was 46%. When Heidenhain pouch dogs received 80 units ACTH intramuscularly daily, there is an increase in both volume and free acid secreted, while with 40 units and 20 units there is an increase in the volume of gastric juice secreted, though it is less than that in those receiving 80 units, with little or no change in free acid. The possible etiology of perforation and bleeding from the Heidenhain pouches which occurred during prednisone or ACTH therapy is discussed.

MALIGNANT MIXED TUMOR OF PAROTID GLAND. G. Fine, and R. B. Marshall. Am. J. Surg. 102:86, 1961.

A case of malignant mixed tumor of the parotid gland with metastases to multiple bones is reported. The mixed character of the tumor was most prominent in the well differentiated, benign appearing femoral metastasis while the primary tumor and local recurrence were predominantly adenomyoepitheliomatous with sparse but well defined myxochondroid components.

PYRIDOXINE IN THE TREATMENT OF HERPES GESTATIONIS. R. P. Fosnaugh, H. G. Bryan, and R. L. Orders. Arch. Dermat. 84:90, 1961.

Four patients with herpes gestationis treated with pyridoxine (vitamin B_6) are reported. The clinical features of herpes gestationis, the metabolism of vitamin B_6,

and the relationship of vitamin B_6 metabolism to the nausea of pregnancy are discussed. The rationale of the use of vitamin B_6 therapy in herpes gestationis and the relationship of this disease to dermatitis herpetiformis are discussed. Studies which might prove helpful in elucidating the pathogenesis of herpes gestationis are outlined. Vitamin B_6 appears to be effective therapy for the subjective and objective findings in herpes gestationis. We employed this therapy in numerous cases of dermatitis herpetiformis without any apparent improvement. The failure of dermatitis herpetiformis to respond to pyridoxine therapy and the failure of herpes gestationis to respond to sulfapyridine therapy is, in our opinion, suggestive evidence that the two diseases represent different metabolic aberrations. The fact that both compounds contain the pyridine nucleus in their structure could indicate closely related pathogeneses. The value of vitamin B_6 in the treatment of nausea of pregnancy and the evidence that a pyridoxine deficiency exists during gestation would appear to make the use of vitamin B_6 in herpes gestationis plausible. We cannot help but wonder whether the widespread use of pyridoxine for nausea of pregnancy has not had a definite effect on the incidence of herpes gestationis. Further studies are indicated. Unfortunately, xanthurenic acid excretion tests were not done in our cases, and blood nonprotein nitrogen was obtained in only one case. The therapeutic value of linolenic acid, low protein, and high fat diets, and the antithyroid drugs and nicotinic acid alone and in combination with vitamin B_6 should be studied.

THE D-LACTIC CYTOCHROME REDUCTASE OF YEAST: ITS CHEMICAL NATURE, ORIGINS, AND RELATION TO THE RESPIRATORY CHAIN. C. GREGOLIN AND T. P. SINGER. Biochem. & Biophys. Res. Comm. 4:189, 1961.

The oxidation of D(-)lactate by cytochrome *c* in cell-free extracts of aerobic yeast cannot be ascribed to either of the known lactic dehydrogenases of yeast and thus the existence of a hitherto unrecognized enzyme was indicated. The enzyme has now been isolated at approximately 500-times the specific activity previously reported for autolysates.

About 90% of the D-lactic cytochrome reductase activity of baker's yeast (Red Star) is recovered in the particles isolated by breaking the cells with a Nossal shaker followed by differential ultracentrifugation. The particles or extracts thereof oxidize D(-)lactate vigorously with either cytochrome *c* or phenazine methosulfate as electron acceptor. Treating the acetone powders of the particles with 4% (w/v) Triton X 100 at pH 6.5 some 60% of the activity is extracted and the resulting extract may be 20-fold purified with calcium phosphate gel treatment, as compared with the particles.

This enzyme has a very restricted specificity. The substrates found to be active are oxidized at pH 7.5 at the following rates relative to D(-)lactate (V_{max} values at

30°, with K_M in parentheses): D(-)lactate, 1 (2.8 x 10 *M*); D-α-hydroxybutyrate, 0.41 (1.4 x 10^{-3}*M*). Anaerobic dialysis of the reductase for 12 hours against 3.5m*M* o-phen-anthroline (or 4 m*M* versene) in 0.01 *M* phosphate, pH 6.5, followed by 3 hours dialysis against 0.01 *M* phosphate, and finally passage through a column of Sephadex G 25 results in complete inactivation of the reductase. Reactivation has been observed at very low concentrations of Zn++, Co++, Mn++, Mg++, and Fe++.

The functioning of cytochrome *c* as an acceptor for the reductase need not indicate that cytochrome *c* is the normal reaction partner of the enzyme in the cell. In fact, D-lactate cannot pass electrons to the respiratory chain under conditions that lead to vigorous oxidation of a genuine respiratory chain-linked substrate, succinate.

RHABDOMYOSARCOMA. R. C. Horn, Jr., and R. B. Patton. Clin. Orthop. No. 19:99, 1961.

Experience with 64 rhabdomyosarcomas is recorded. They have been divided into pleomorphic, alveolar, embryonal and botryoid subclassifications. The pleomorphic tumors were predominantly lesions of the extremities. The alveolar rhabdomyosarcomas were evenly distributed in the extremities, the trunk, the head and the neck, and the genito-urinary system. The embryonal tumors were predominantly of the genitourinary tract and/or the pelvis and of the head and the neck. The botryoid sarcomas predominated in the head and the neck; all arose beneath the mucous membrane of a hollow viscus or body cavity. The rhabdomyosarcomas are predominantly tumors of males and usually of younger age groups, the average age being 26.8 years. The highly malignant clinical behavior of the rhabdomyosarcoma is emphasized by this experience. It is suggested that prompt recognition of the tumor, together with full realization of its high malignant potential and the prompt institution of radical surgery, where possible, offers some hope in the future for the patient with rhabdomyosarcoma. Unfortunately, less than one third of the rhabdomyosarcomas studied have occurred in extremities, the location best lending itself to truly radical treatment.

PROTEIN ALLOWANCE IN INFANCY AND CHILDHOOD. J. A. Johnston, M. J. Sweeney, R. C. Brown, J. W. Maroney, and G. Manson. J. Pediat. 59:47, 1961.

Infants were fed isocaloric treated milk mixtures whose protein content provided 8, 13, 15, 20, and 25 per cent of the calories; the increase in calories from protein was compensated for by a comparable decrease in calories derived from carbohydrate. The increased intake of protein from 8 per cent to higher levels was accompanied by increased nitrogen retention; however, there were no statistically

significant differences between the retentions on intakes of which the proportions of calories from protein were 13, 15, and 20 per cent, respectively. Higher retentions of nitrogen were noted with a diet containing 25 per cent of calories as protein, but in the absence of determinations of blood nitrogen the interpretation of the observation at this level is not possible. Infants who received milk formulas containing a low percentage of calories from protein took significantly larger amounts of the formulas than did those who received mixtures with a higher percentage of protein. The weight gained per unit of nitrogen retained is significantly higher on mixtures deriving 8 per cent of the calories from protein than on mixtures containing higher percentages of protein and lower percentages of carbohydrate. The differences are not significant when comparisons are made among mixtures deriving 13, 15, and 20 per cent of the calories from protein.

STUDIES ON CHOLINE DEHYDROGENASE: ORGANIZATION OF THE RESPIRATORY CHAIN IN CHOLINE OXIDASE. T. KIMURA, T. P. SINGER, AND C. J. LUSTY. Biochem. & Biophys. Acta, 44:284, 1960.

Titration of rat-liver mitochondria with azide, antimycin A, 2-n-heptyl-4-hydroxyquinoline N-oxide, and cyanide showed quantitatively very different effects on succinic and on choline oxidase activities. The former enzyme system was very much more sensitive to each of these inhibitors and reached complete inhibition at relatively low concentrations of these inhibitors; the latter showed a significant activity even at high concentrations of all the inhibitors except cyanide. While choline oxidase was partially resistant to antimycin A and quinoline oxide, the reduction of cytochrome c by choline was completely inhibited. Added cytochrome c stimulated succinate oxidation several fold without affecting choline oxidase. Anaerobically, no oxidation of choline by fumarate could be demonstrated. In untreated rat-liver mitochondria the succinic and choline oxidase and the corresponding cytochrome c reductase activities are additive, not competitive. When the amount of active cytochrome a_3 was limited by titration with azide, the competition of succinic and choline dehydrogenases for the respiratory chain could be demonstrated. Limitation of the rate of the cytochrome b to c_1 step by antimycin A or quinoline oxide, however, failed to produce competition between the two oxidases. The differential effects of respiratory chain inhibitors and of added cytochrome c were shown to be due to the greater activity of succinic oxidase, as compared with choline oxidase. Following equalization of the activities of the two enzyme systems by titration with malonate these differences disappeared largely, but not entirely. The conditions necessary for the development of the inhibitor-resistant oxidation of choline have been studied. With excess azide present, choline and succinic oxidases compete for the azide-resistant, autooxidizable component. With excess antimycin A or quinoline oxide present,

however, succinate oxidation is completely abolished, but significant choline oxidase activity remains. On the basis of these observations, a scheme has been presented for the interrelations of the choline and succinic oxidase chains in liver mitochondria. It is proposed that the two oxidases operate through respiratory chains which are interlinked between cytochrome c_1 and o_2, but not at the oxidation level of cytochrome b. It is suggested that the b component of the choline chain may become autooxidizable under suitable conditions and thus account for the incomplete inhibition of choline oxidase by respiratory chain inhibitors.

PHYSICAL THERAPY IN THE TREATMENT OF STRAINS, SPRAINS, AND CONTUSIONS IN INDUSTRY. B. P. LaChapelle. Physical Therapy Rev. 41:505, 1961.

Although it seems incredible, it is true that many industries, particularly the automotive industries, have been spending millions of dollars in the past few years to increase the percentage of strains, sprains, and contusions in their factories. This has, of course, been a secondary rather than a primary result. With their intensive safety campaigns and research programs, they unquestionably have made great strides in the prevention of the major industrial accidents such as amputations, peripheral nerve injuries, and spinal cord injuries. But their new safety measures have, in turn, contributed to an increased production rate. Along with this, there has been an increase in what is referred to in industry as "microtrauma" or repetitive motion strain. Greater production has also increased the number of sprains and contusions resulting from the more rapid movements and greater co-ordination required by the workers operating machinery in the production lines. The so-called minor injuries may be classified under the three main categories: sprains, strains, and contusions. Proper diagnosis, early and adequate treatment, adequate equipment and competent personnel are of major importance in the treatment of strains, sprains, and contusions. With these available an early return to the fullest possible function should be easily attained and compensation payments should be greatly reduced.

NONCHROMAFFIN PARAGANGLIOMA: A COMPARATIVE STUDY. R. B. Marshall, and R. C. Horn, Jr. Cancer 14:779, 1961.

Nineteen tumors of carotid and jugular body have been studied clinically, morphologically, and histochemically and compared with normal carotid bodies and nosologically related tumors. Tumors of the carotid, jugular, aortic bodies, the vagal nodose ganglion, and retroperitoneum appear closely related. The alveolar soft part sarcoma appears distinct. The cerebellar hemangioblastoma requires further study before it can definitely be excluded as a member of this group. A possible relationship between the alveolar soft part sarcoma and the rhabdomyosarcoma of alveolar type is suggested.

STREPTOMYCIN SULFATE AND DIHYDROSTREPTOMYCIN TOXICITY. T. M. McGEE. Tr. Am. Acad. Ophth. 65:222, 1961.

The lesion in streptomycin and dihydrostreptomycin toxicity is limited to the inner ear. Streptomycin sulfate and dihydrostreptomycin both damage the vestibular end organ. They do so in a selective manner in the cat, where the cristae appear to be less resistant to toxic changes than do the maculas of the saccule and the utricle. Dihydrostreptomycin toxicity is associated with a delayed permanent loss of hearing which can occur several weeks to several months following treatment with the drug.

GASTROSCOPIC DIAGNOSIS OF LYMPHOMA OF THE STOMACH. B. M. SCHUMAN. Bull. Gastrointestinal Endoscopy 8:8, 1961.

A report of a case of primary reticulum cell sarcoma of the stomach is presented. The gastroscopist failed to recognize the true nature of the tumor and the gastroscopic biopsy did not demonstrate malignant change. Analysis of the literature indicates that gastroscopic visualization is an inadequate basis on which to infer the cellular type of a malignant growth. Biopsy through the flexible operating gastroscope is the best available method of establishing the diagnosis of gastric lymphoma, but the nature of the tumor is such that it is not readily accessible to mucosal biopsy, particularly as an early growth. It is incumbent upon the gastroscopist to make every effort to provide a pathologic diagnosis so that appropriate therapy may be planned.

STINGING INSECTS: A THREAT TO LIFE. J. H. SHAFFER. J.A.M.A. 177:473, 1961.

Various kinds of insects can cause various symptoms. Inhalation of body proteins and emanations of butterflies, caddis flies, moths, May flies, and bees and other flying insects may cause allergic symptoms of the respiratory tract. Protection may, in most instances, be furnished by desensitization with insect whole body extracts. Bites from insects such as chiggers, ants, mosquitoes, gnats, fleas, houseflies, and other flies may cause local trauma only, or local and systemic allergic symptoms. Desensitization with insect whole body extracts may again be helpful in prevention of such allergic symptoms. The most violent allergic reactions are caused by stings from insects of the Hymenoptera group (honeybees, bumblebees, wasps, yellow and black hornets, and yellow jackets). Persons who have been stung and have experienced mild to moderate local reactions only, may not need desensitization. Those persons who have experienced severe local and/or generalized allergic reactions from previous stings should, however, receive desensitization therapy with polyvalent insect whole body extracts. Although desensitization is effective in approximately

95% of the patients treated, it is well to furnish all patients who are allergic to insects with an emergency kit along with specific instructions as to its use. This kit should be readily available to the patient whether at home, on vacation trips, or in pursuit of daily activities. Sudden death from anaphylaxis is a real threat to human life when persons, once sensitized to the protein substances of stinging insects, are re-stung. Effective emergency treatment and desensitization therapy can, in most instances, nullify this threat to life.

REITER'S SYNDROME: A REVIEW OF CLINICAL FEATURES AND STUDIES ON ETIOLOGY. J. T. SHARP. M. Clin. North America 45:1325, 1961.

Reiter's syndrome has in the past been considered a unique association of arthritis, urethritis and conjunctivitis. Other clinical features which have been frequently encountered are iritis, keratodermia, balanitis circinata and myocarditis. Many cases of urethritis or dysentery associated with some clinical features of the Reiter's syndrome, but lacking the full triad, probably represent the same disease process, but at the present time there are insufficient clinical data available to determine what diagnostic criteria would be most inclusive without sacrificing accuracy of diagnosis. Studies on etiology in this condition have not succeeded in defining the cause or pathogenisis.

MALIGNANT GANGLIONEUROMA: REPORT OF A CASE OF AN AGGRESSIVELY GROWING IMMATURE GANGLIONEUROMA. K. J. SHIER, A. K. SHAALAN, AND R. C. HORN, JR. Canad. M.A.J. 85:135, 1961.

A case of an aggressively growing immature ganglioneuroma in a three-year-old white girl is reported. Despite large areas of advanced differentiation and absence of distinct neuroblastomatous features, the tumor proved to be highly malignant in so far as local growth is concerned. The fact that immature ganglioneuromas are on record that have pursued a considerably more benign course, indicates that the prognostic significance of the degree and extent of cellular differentiation is limited.

RAPID METHOD FOR OBTAINING HEMATOXYLIN AND EOSIN BIOPSY OF BONE FOR TABLE DIAGNOSIS. A. R. VILLANUEVA, AND H. M. FROST. Am. J. Clin. Path. 36:54, 1961.

A rapid, reliable, and simplified method of making decalcified sections and staining them with hematoxylin and eosin for table diagnosis is described. Cellular structures are better preserved with this method than with the conventional paraffin methods. Slides can be retained permanently. Danger of too much decalcification is minimized. Embedding in paraffin and sectioning with a microtome are not utilized.

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